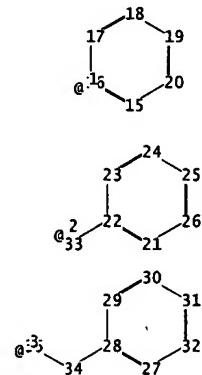
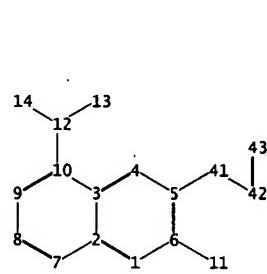
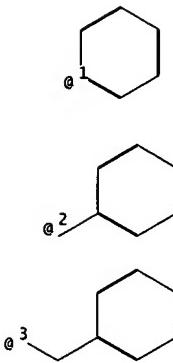
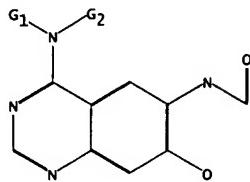


10/016, 280



chain nodes :

11 12 13 14 33 34 35 41 42 43

ring nodes :

2 3 4 5 6 7 8 9 10 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
30 31 32

chain bonds :

5-41 6-11 10-12 12-13 12-14 22-33 28-34 34-35 41-42 42-43

ring bonds :

1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 15-16 15-20 16-17 17-18 18-19
19-20 21-22 21-26 22-23 23-24 24-25 25-26 27-28 27-32 28-29 29-30 30-31 31-32

exact/norm bonds :

5-41 6-11 10-12 12-13 12-14 41-42 42-43

exact bonds :

22-33 28-34 34-35

normalized bonds :

1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 15-16 15-20 16-17 17-18 18-19
19-20 21-22 21-26 22-23 23-24 24-25 25-26 27-28 27-32 28-29 29-30 30-31 31-32

isolated ring systems :

containing 1 : 15 : 21 : 27 :

G1:H,Ak

G2:[*1], [*2], [*3]

Hydrogen count :

8:= exact 1

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom
22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom 31:Atom
32:Atom 33:CLASS 34:CLASS 35:CLASS 41:CLASS 42:CLASS 43:CLASS

10/ 016,280

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 "Ask CAS" for self-help around the clock
NEWS 3 SEP 01 INPADOC: New family current-awareness alert (SDI) available
NEWS 4 SEP 01 New pricing for the Save Answers for SciFinder Wizard within
STN Express with Discover!
NEWS 5 SEP 01 New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
NEWS 6 SEP 27 STANDARDS will no longer be available on STN
NEWS 7 SEP 27 SWETSCAN will no longer be available on STN
NEWS 8 OCT 28 KOREAPAT now available on STN
NEWS 9 NOV 18 Current-awareness alerts, saved answer sets, and current
search transcripts to be affected by CERAB, COMPUAB, ELCOM,
and SOLIDSTATE reloads
NEWS 10 NOV 30 PHAR reloaded with additional data

NEWS EXPRESS OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT
MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * STN Columbus * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:07:18 ON 30 NOV 2004

=> file reg
COST IN U.S. DOLLARS
FULL ESTIMATED COST

| SINCE ENTRY | TOTAL SESSION |
|-------------|---------------|
| 0.21 | 0.21 |

FILE 'REGISTRY' ENTERED AT 14:07:50 ON 30 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file

10/ 016,280

provided by InfoChem.

STRUCTURE FILE UPDATES: 28 NOV 2004 HIGHEST RN 790189-55-8
DICTIONARY FILE UPDATES: 28 NOV 2004 HIGHEST RN 790189-55-8

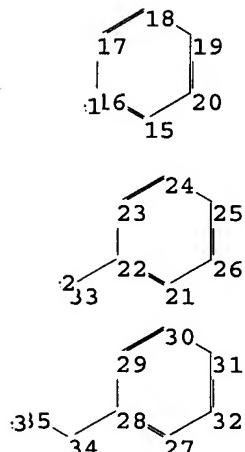
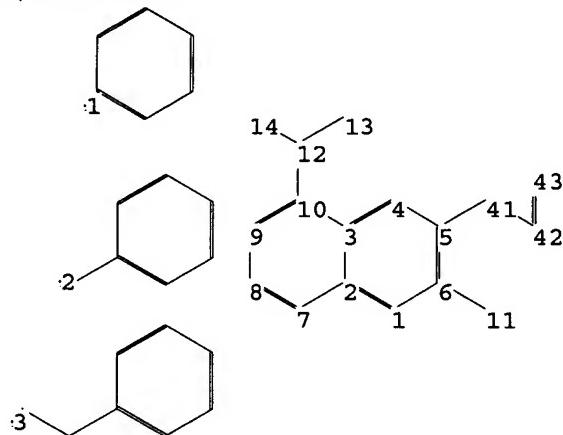
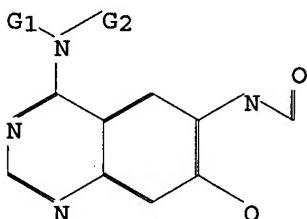
TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

>>
Uploading C:\STNEXP4\QUERIES\10016280.str



chain nodes :
11 12 13 14 33 34 35 41 42 43
ring nodes :
1 2 3 4 5 6 7 8 9 10 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29
30 31 32
chain bonds :
5-41 6-11 10-12 12-13 12-14 22-33 28-34 34-35 41-42 42-43
ring bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 15-16 15-20 16-17 17-18
18-19 19-20 21-22 21-26 22-23 23-24 24-25 25-26 27-28 27-32 28-29 29-30 30-31
31-32
exact/norm bonds :
5-41 6-11 10-12 12-13 12-14 41-42 42-43
exact bonds :
22-33 28-34 34-35
normalized bonds :
1-2 1-6 2-3 2-7 3-4 3-10 4-5 5-6 7-8 8-9 9-10 15-16 15-20 16-17 17-18
18-19 19-20 21-22 21-26 22-23 23-24 24-25 25-26 27-28 27-32 28-29 29-30 30-31
31-32
isolated ring systems :
containing 1 : 15 : 21 : 27 :

G1:H,Ak

10/ 016,280

G2:[*1], [*2], [*3]

Hydrogen count :

8:= exact 1

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS
12:CLASS 13:CLASS 14:CLASS 15:Atom 16:Atom 17:Atom 18:Atom 19:Atom 20:Atom
21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:Atom 30:Atom
31:Atom 32:Atom 33:CLASS 34:CLASS 35:CLASS 41:CLASS 42:CLASS 43:CLASS

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

=> s l1 ful

FULL SEARCH INITIATED 14:08:15 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 437 TO ITERATE

100.0% PROCESSED 437 ITERATIONS
SEARCH TIME: 00.00.03

422 ANSWERS

L2 422 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS
FULL ESTIMATED COST

| SINCE FILE ENTRY | TOTAL SESSION |
|------------------|---------------|
| 155.42 | 155.63 |

FILE 'CAPLUS' ENTERED AT 14:08:26 ON 30 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 30 Nov 2004 VOL 141 ISS 23
FILE LAST UPDATED: 29 Nov 2004 (20041129/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 12

L3 73 L2

L3 ANSWER 1 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:965067 CAPLUS
 TITLE: Combinations for the treatment of diseases involving cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis
 INVENTOR(S): Hilberg, Frank; Solca, Flavio; Stefanic, Martin; Friedrich, Baum, Anke; Munzert, Gerd; Van Meel, Jacobus C. A.
 PATENT ASSIGNEE(S): Boehringer Ingelheim International G.m.b.H., Germany; Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.
 SOURCE: PCT Int. Appl., 101 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2004096224 | A2 | 20041111 | WO 2004-EP4363 | 20040424 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1473043 | A1 | 20041103 | EP 2003-9587 | 20030429 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| PRIORITY APPLN. INFO.: | | | EP 2003-9587 | A 20030429 |
| | | | EP 2004-508 | A 20040113 |
| | | | EP 2004-1171 | A 20040121 |

AB The present invention relates to a pharmaceutical combination for the treatment of diseases which involves cell proliferation, migration or apoptosis of myeloma cells, or angiogenesis. The invention also relates to a method for the treatment of said diseases, comprising co-administration of effective amts. of specific active compds. and/or co-treatment with radiation therapy, in a ratio which provides an additive and synergistic effect, and to the combined use of these specific compds. and/or radiotherapy for the manufacture of corresponding pharmaceutical combination preps. The pharmaceutical combination can include selected protein tyrosine kinase receptor antagonists and further chemotherapeutic or naturally occurring semisynthetic or synthetic agents.

IT INDEXING IN PROGRESS

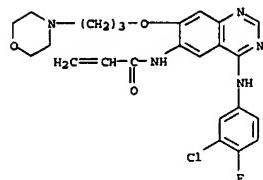
IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (drug combinations for diseases involving cell proliferation and migration or apoptosis or angiogenesis including protein tyrosine kinase receptor antagonists and radiotherapy)

RN 289499-45-2 CAPLUS

CN 2-Propanamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-

L3 ANSWER 1 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 morpholinyl)propoxy]-6-quinazolinyl-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L3 ANSWER 2 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:902075 CAPLUS
 DOCUMENT NUMBER: 141:361105
 TITLE: Methods for detection of ErbB cell surface receptor complexes as cancer biomarkers and therapeutic effectiveness of cleavage thereof
 INVENTOR(S): Chan-Hui, Po-Ying; Salimi-Moosavi, Hosseini; Shi, Yining; Singh, Sharad; Dua, Rajiv; Mukherjee, Ali; Pidaparthi, Sailleja; Aclara Biosciences, Inc., USA
 PATENT ASSIGNEE(S): Aclara Biosciences, Inc., USA
 SOURCE: PCT Int. Appl., 108 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 29
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2004091384 | A2 | 20041028 | WO 2004-US9715 | 20040330 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SV, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004126818 | A1 | 20040701 | US 2003-623057 | 20030717 |
| PRIORITY APPLN. INFO.: | | | US 2003-459888P | P 20030401 |
| | | | US 2003-623057 | A 20030717 |
| | | | US 2003-494482P | P 20030811 |
| | | | US 2003-508034P | P 20031001 |
| | | | US 2003-512941P | P 20031020 |
| | | | US 2003-523258P | P 20031118 |
| | | | US 2002-398724P | P 20020725 |

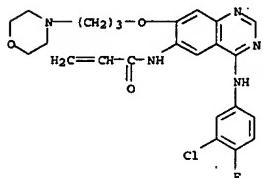
AB The invention is directed to a new class of biomarker in patient samples comprising dimers of ErbB cell surface membrane receptors. In one aspect, the invention includes a method of determining the status of a disease or healthful condition by correlating such condition to amts. of one or more dimers of ErbB cell surface membrane receptors measured directly in a patient sample, in particular a fixed tissue sample. In another aspect, the invention includes a method of determining a status of a cancer in a specimen from an individual by correlating measurements of amts. of one or more dimers of ErbB cell surface membrane receptors in cells of the specimen to such status, including presence or absence of a pre-cancerous state, presence or absence of a cancerous state, prognosis of a cancer, or responsiveness to treatment. Preferably, methods of the invention are implemented by using sets of binding compds. having releasable mol. tags that are specific for multiple components of one or more types of receptor dimers. After binding, mol. tags are released and separated from the assay mixture for anal.

IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(methods for detection of ErbB cell surface receptor complexes as cancer biomarkers and therapeutic effectiveness of cleavage thereof)

L3 ANSWER 2 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 CN 2-Propanamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L3 ANSWER 3 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:719893 CAPLUS
 DOCUMENT NUMBER: 141:243560
 TITLE: Preparation of 4-anilinoquinazolines as tyrosine kinase inhibitors for the treatment of tumors
 INVENTOR(S): Himmelbach, Frank; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
 SOURCE: Ger. Offen., 21 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|----------|
| DE 10307165 | A1 | 20040902 | DE 2003-10307165 | 20030220 |
| WO 2004074263 | A1 | 20040902 | WO 2004-EPI398 | 20040214 |
| W: AE, AE, AG, AL, AL, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BZ, BZ, CA, CH, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DK, DK, DM, DZ, EC, EC, EE, ES, EG, ES, FI, FI, GB, GD, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI, NI, NO
RW: BW, GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| PRIORITY APPLN. INFO.: DE 2003-10307165 A 20030220 | | | | |
| OTHER SOURCE(S): MARPAT 141:243560
GI | | | | |

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = H, alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3 = H, halo, OH, etc.; R4, R5 = H, alkyl; X = C(CN), N with provisos; Z = (un)substituted heterocycle] and their pharmaceutically acceptable salts and formulations were prepared. For example, coupling of 4-[2,2-dimethoxyethyl]homomorpholine and N4-(3-chloro-4-fluorophenyl)-7-[(3S)-tetrahydro-3-furanyl]oxy-4,6-quinoxalinediamine and N4-(3-chloro-4-fluorophenyl)-7-[(3S)-tetrahydro-3-furanyl]oxy-4,6-quinoxalinediamine III in 63% yield. In human epidermal growth factor receptor binding assays, anilinoquinazoline III exhibited an IC50 value of 1.5 nM. Compds. I are claimed useful for the treatment of tumors, i.e., prostate benign hyperplasia.

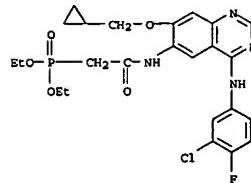
IT 365532-31-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 4-anilinoquinazolines as tyrosine kinase inhibitors for the treatment of tumors)

RN 365532-31-6 CAPLUS

CN Phosphonic acid, [2-[(4-((3-chloro-4-fluorophenyl)amino)-7-

L3 ANSWER 3 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 (cyclopropylmethoxy)-6-quinoxolinyl(amino)-2-oxoethyl]-, diethyl ester
 (9CI) (CA INDEX NAME)



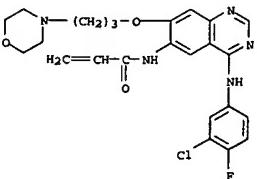
L3 ANSWER 4 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:717320 CAPLUS
 DOCUMENT NUMBER: 141:288467
 TITLE: Canertinib (Pfizer)
 AUTHOR(S): Galmarini, Carlos Maria
 CORPORATE SOURCE: INSERM 590, 8, University of Lyon, Lyon, 69373/08, Fr.
 SOURCE: IDrugs (2004), 7(1), 58-63
 CODEN: IDRUPN; ISSN: 1369-7056
 PUBLISHER: Thomson Scientific
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. Canertinib, a water-soluble, orally available analog of PD-169414, is an epidermal growth factor tyrosine kinase inhibitor under development by Pfizer Inc as a potential treatment for cancer. This article describes the synthesis and structure-activity relations of the compound, its preclin. development, metabolism and pharmacokinetics, toxicity, clin. development, and side effects and contraindications.

IT 267243-28-7P, Canertinib

RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and pharmacol. of canertinib, an angiogenesis inhibitor (epidermal growth factor inhibitor), for the treatment of cancer)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-(4-((3-chloro-4-fluorophenyl)amino)-7-[(4-
morpholinyl)propoxy]-6-quinoxolinyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

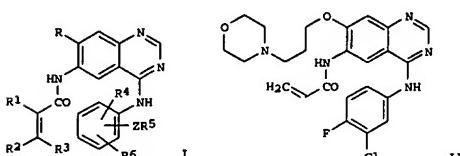
L3 ANSWER 5 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:654786 CAPLUS
 DOCUMENT NUMBER: 141:17186
 TITLE: Preparation of substituted quinoxolines for use in pharmaceutical compositions as inhibitors of tyrosine kinases
 INVENTOR(S): Barth, Hubert; Bridges, Alexander James; Heemstra, Ronald J.; Horne, Nicole Marcia; Hughes, Robert Craig; Jacks, Thomas Elliott; McNamara, Dennis Joseph; Schneider, Simon; Steiner, Klaus; Toogood, Peter Laurence; Winters, Roy Thomas

PATENT ASSIGNEES(S): Germany
U.S. Pat. Appl. Publ., 32 pp.

SOURCE: CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| US 2004/58065 | A1 | 20040812 | US 2004-771774 | 20040204 |
| WO 2004069791 | A1 | 20040819 | WO 2004-IB321 | 20040203 |
| W: AE, AE, AG, AL, AL, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BZ, BZ, CA, CH, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DB, DE, DK, DK, DM, DZ, EC, EC, ES, ES, FI, FI, GB, GD, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, MZ, NA, NI, NO
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, ER, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| NL 1025414 | | | | |
| NL 1025414 A1 20040806 NL 2004-1025414 20040205 | | | | |
| PRIORITY APPLN. INFO.: US 2003-445095P OTHER SOURCE(S): MARPAT 141:17186
GI | | | | |

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



AB Quinoxoline amines, such as I [R1, R2, R3 = H, NO2, halogen, alkyl, alkenyl, alkyne, cycloalkyl, heterocyclic, carboxy, etc.; R4, R6 = H, OH, CN, NO2, CF3, halogen, alkyl, alkoxy, alkylamino, alkylthio, alkylsulfinyl, acyl, carbamoyl, etc.; R5 = aryl or heteroaryl, such as Ph, pyridyl,

L3 ANSWER 5 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 furyl, thiazolyl, etc.; ZR5 = H, halogen; Z = linking group, such as alkylene, etc.; R = OH, SH, NH₂, heterocyclylalkyloxy, etc.) were prepd. for therapeutic use as inhibitors of tyrosine kinase and may be useful for treatment of cancer, restenosis, atherosclerosis, endometriosis and psoriasis. Thus, N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)-quinazolin-6-yl]-acrylamide(I) was prepd. via a series of synthetic steps starting from acryloyl chloride, 3-(morpholin-4-yl)propan-1-ol, 3-chloro-4-fluoroaniline, and 4-chloro-7-fluoro-6-nitroquinazoline.

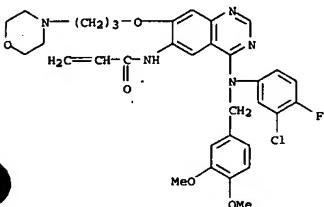
IT 736173-03-8P

RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of substituted quinazolines for use in pharmaceutical compns. as inhibitors of tyrosine kinases)

RN 736173-03-8 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)[(3,4-dimethoxyphenyl)methyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 6 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:633433 CAPLUS

DOCUMENT NUMBER: 141:167750

TITLE: Novel irreversible inhibitors of epidermal growth factor receptor tyrosine kinase and uses thereof for therapy and diagnosis
 INVENTOR(S): Mishani, Eyal; Rozen, Yulia; Abourbeh, Galith; Levitzki, Alexander
 PATENT ASSIGNEE(S): T.K. Signal Ltd., Israel
 SOURCE: PCT Int. Appl., 98 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2004064718 | A2 | 20040805 | WO 2004-1168 | 20040122 |
| W: AE, AE, AG, AL, AL, AM, AM, AT, AU, AZ, AZ, BB, BG, BR, BR, BY, BY, BZ, BZ, CA, CH, CN, CO, CO, CR, CU, CU, CZ, CZ, DE, DE, DK, DM, DZ, EC, EC, EE, EG, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, MZ, NA, NI | | | | |

PRIORITY APPLN. INFO.: US 2003-441779P P 20030123

OTHER SOURCE(S): MARPAT 141:167750

AB Novel epidermal growth factor receptor tyrosine kinase (EGFR-TK) irreversible inhibitors, pharmaceutical compns. including same and their use in the treatment of EGFR-TK related diseases or disorders are disclosed. Novel radiolabeled EGFR-TK irreversible inhibitors as their use as biomarkers for medicinal radioimaging such as Positron Emission Tomog. (PET) and Single Photon Emission Computed Tomog. (SPECT) and as radiopharmaceuticals for radiotherapy are further disclosed.

IT 733009-47-7P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(inhibitors of EGFR tyrosine kinase for cancer therapy and diagnosis)

RN 733009-47-7 CAPLUS

CN Acetamide, 2-chloro-N-[4-[(4,5-dichloro-2-(fluoro-18F)phenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 6 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

ACCESSION NUMBER: 2004:533970 CAPLUS

DOCUMENT NUMBER: 141:65088

TITLE: Methods and compositions for the prevention or treatment of neoplasia comprising a COX-2 inhibitor in combination with an epidermal growth factor receptor antagonist

INVENTOR(S): Masferrer, Jaime

PATENT ASSIGNEE(S): Pharmacia Corporation, USA

SOURCE: U.S. Pat. Appl. Publ., 103 pp., Cont.-in-part of U.S. Ser. No. 470,951.

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 21

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 2004127470 | A1 | 20040701 | US 2003-651916 | 20030829 |
| PRIORITY APPLN. INFO.: | | | US 1998-113786P | P 19981223 |
| | | | US 1999-470951 | B2 19991222 |

AB The present invention relates to a novel method of preventing and/or treating neoplasia disorders in a subject that is in need of such prevention or treatment by administering to the subject at least one COX-2 inhibitor in combination with an EGFR receptor antagonist. Compns., pharmaceutical compns. and kits are also described.

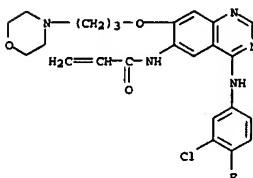
IT 267243-28-7

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(as EGFR antagonist; COX-2 inhibitor in combination with epidermal growth factor receptor antagonist for prevention or treatment of neoplasia)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L3 ANSWER 8 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:533967 CAPLUS
 DOCUMENT NUMBER: 141:65147
 TITLE: Method for treating diseases associated with abnormal tyrosine kinase activity by administering a DNA methylation inhibitor and a tyrosine kinase inhibitor
 INVENTOR(S): Lyons, John; Rubinfeld, Joseph
 PATENT ASSIGNEE(S): U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of U.S. Ser. No. -71,849.
 SOURCE: CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| US 2004127453 | A1 | 20040701 | US 2002-206854 | 20020726 |
| US 2003147813 | A1 | 20030807 | US 2002-71849 | 20020207 |
| WO 2003065995 | A2 | 20030814 | WO 2003-US3537 | 20030206 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, US, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, TF, BG, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 2002-71849 A2 20020207
 US 2002-206854 A1 20020726

AB Methods are provided for treating diseases associated with abnormal activity of kinases. The method comprises: administering a DNA methylation inhibitor to the patient in therapeutically effective amount; and administering a kinase inhibitor to the patient in therapeutically effective amount, such that the in vivo activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat cancer associated with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (PI3K), protein kinases including serine/threonine kinases such as Raf kinases, protein kinase kinases such as MEK, and tyrosine kinases such as those in the epidermal growth factor receptor family (EGFR), platelet-derived growth factor receptor family (PDGFR), vascular endothelial growth factor receptor (VEGFR) family, nerve growth factor receptor family (NGFR), fibroblast growth factor receptor family (FGFR) insulin receptor family, ephrin receptor family, Met receptor family, Ror family, c-kit family, Src family, Fes family, JAK family, Fak family, Btk family, Syk/ZAP-70 family, and Ab1 family.

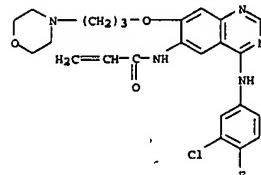
IT 289499-45-2, C11033

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as EGFR tyrosine kinase inhibitor; treating diseases associated with abnormal tyrosine kinase activity by administering DNA methylation inhibitors and tyrosine kinase inhibitors)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-

L3 ANSWER 8 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L3 ANSWER 9 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:430979 CAPLUS
 DOCUMENT NUMBER: 141:5495
 TITLE: Altered patterns of protein phosphorylation associated with glioblastoma progression and their diagnostic detection with phospho-specific antibodies
 INVENTOR(S): Mischel, Paul S.; Sawyers, Charles L.; Smith, Bradley L.; Crosby, Katherine
 PATENT ASSIGNEE(S): The Regents of the University of California, USA; Cell Signaling Technology, Inc.
 SOURCE: PCT Int. Appl., 90 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2004044218 | A2 | 20040527 | WO 2003-US35115 | 20031105 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, TF, BG, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004106141 | A1 | 20040603 | US 2003-701490 | 20031105 |
| PRIORITY APPLN. INFO.: | | | US 2002-423777P | P 20021105 |

AB Proteins showing altered patterns of phosphorylation are identified for use in the diagnosis of gliomas, including glioblastoma multiforme. The proteins showing altered patterns of phosphorylation may also be targets for chemotherapy.

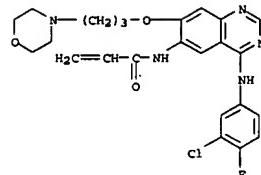
IT 289499-45-2, C1 1033

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (in treatment of glioma, selection of, altered patterns of protein phosphorylation associated with glioblastoma progression and their diagnostic detection with phospho-specific antibodies)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 9 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

L3 ANSWER 10 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:24391 CAPLUS
 DOCUMENT NUMBER: 141:49704
 TITLE: Induction of apoptosis by ionizing radiation and CI-1033 in HuCCT-1 cells
 AUTHOR(S): Murakami, Masateru; Sasaki, Tamito; Yamasaki, Souichirou; Kuwahara, Kenichi; Miyata, Hideki; Chayama, Kazuki
 CORPORATE SOURCE: Graduate School of Biochemical Sciences, Programs for Biochemical Research, Division of Frontier Medical Science, Department of Medicine and Molecular Science, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan
 SOURCE: Biochemical and Biophysical Research Communications (2004), 319(1), 114-119
 PUBLISHER: Elsevier Science
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB CI-1033 is a quinazoline-based HER family tyrosine kinase inhibitor that is currently being evaluated as a potential anticancer agent. The present study examined the mol. mechanism by which CI-1033 induces apoptosis either as a single agent or in combination with radiation. Although CI-1033 alone did not induce apoptosis, the simultaneous exposure of cells to CI-1033 and radiation induced significant levels of apoptosis. The sequential treatment of cells with CI-1033 followed by radiation induced an even greater effect with 62.6% of cells undergoing apoptosis but this enhanced effect was not seen if cells were treated first with radiation and then CI-1033. The combination treatment induces apoptosis of HuCCT-1 via upregulation of FasL and Bid cleavage. These data suggest that modulation of the Fas-FasL pathway and activation of Bid could be useful for increasing the anti-tumor effect of CI-1033 in this type of cancer.

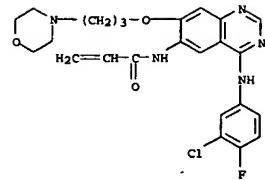
IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (apoptosis induction by TK inhibitor CI-1033 alone or in combination with ionizing irradiation: FasL and Bid cleavage upregulation)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl], dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 10 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:392613 CAPLUS
 DOCUMENT NUMBER: 140:388248
 TITLE: Nucleotide-binding protein-directed probes and their use in determining enzyme profiles
 INVENTOR(S): Campbell, David Alan; Szardenings, Anna Katrin; Shredler, Kevin Robert; Betancort, Juan Manuel; Winn, David
 PATENT ASSIGNEE(S): Activx Biosciences, Inc., USA
 SOURCE: PCT Int. Appl., 131 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2004040003 | A2 | 20040513 | W0 2003-U34550 | 20031029 |
| W: AE, AG, AL, AM, AT, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, ES, EG, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MM, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, ES, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GG, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 2002-422304P P 20021029
 AB The present invention provides nucleotide binding protein-directed affinity probes (NBAPs), such as derive of 4-phenylaminquinazoline, staurosporine, bis-indoleimide, pyrido[2,3-d]pyrimidine, and adenine, and methods for their use. The NBAP generally comprises the aforementioned targeting moiety, a reactive group (thiocyanate, maleimide, etc.), and a label (fluorescein, rhodamine, etc.). The subject methods and compus, can provide enhanced simplicity and accuracy in identifying changes in the presence, amount, or activity of nucleotide binding proteins in a complex protein mixture, preferably kinases, and most preferably active forms of kinases, using NBAPs that bind to target nucleotide binding protein(s).

IT 688024-56-8

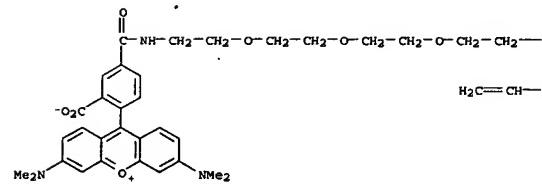
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
 (nucleotide-binding protein-directed probes and their use in determining enzyme profiles)

RN 688024-56-8 CAPLUS

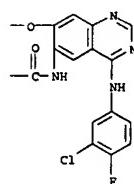
CN Xanthylum, 9-(2-carboxy-4-[(4-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyloxy)-1-oxo-5,8,11-trioxa-2-azatridec-1-yl]phenyl)-3,6-bis(dimethylamino)-, inner salt (9CI) (CA INDEX NAME)

L3 ANSWER 11 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-A



PAGE 1-B



L3 ANSWER 12 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:354796 CAPLUS

DOCUMENT NUMBER: 140:368653

TITLE: Endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for the treatment of cancer

INVENTOR(S): Boyle, Francis Thomas; Curwen, Jon Owen; Gallagher, Neil James; Hancock, Ursula Joy; Hughes, Andrew Mark; Johnstone, Donna; Taylor, Sian Tomiko; Tonge, David William

PATENT ASSIGNEE(S): AstraZeneca AB, Swed.; AstraZeneca UK Limited

SOURCE: PCT-Int. Appl., 24 pp.

CODEN: PIKXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|----------|
| WO 2004035057 | A1 | 20040429 | WO 2003-GB4347 | 20031007 |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, BY, KG, KZ, MD | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, S2, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | |

PRIORITY APPLN. INFO.: GB 2002-23854 A 20021012
 AB A combination, comprising an endothelin receptor antagonist (e.g. ZD4054), or a pharmaceutically acceptable salt thereof, and an EGF receptor tyrosine kinase inhibitor (e.g. ZD1839), or a pharmaceutically acceptable salt thereof, is described. The combination of the invention is useful for the treatment of cancer, e.g. prostate cancer.

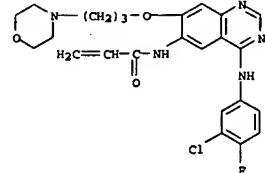
IT 267243-28-7

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (endothelin receptor antagonist-EGF receptor tyrosine kinase inhibitor combination for treatment of cancer)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinoxolinyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 12 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:280687 CAPLUS

DOCUMENT NUMBER: 140:296746

TITLE: Epidermal growth factor receptor inhibitors: a new perspective in the treatment of lung cancer

AUTHOR(S): Tiseo, M.; Loprevite, M.; Ardizzi, A.
 CORPORATE SOURCE: Division of Medical Oncology A Istituto Nazionale per la Ricerca sul Cancro Genova, Genoa, 16132, Italy
 SOURCE:

Current Medicinal Chemistry: Anti-Cancer Agents (2004), 4(2), 139-148

CODEN: CMCACI; ISSN: 1568-0118

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Lung cancer is the leading cause of death worldwide. Current treatment modalities, including chemotherapy, radiotherapy and surgery, provide only limited improvement in the natural course of this disease. Therefore, the development of new therapeutic strategies is highly awaited. This review focuses on recent achievements on a novel class of anticancer drugs targeting the EGFR (Epidermal Growth Factor Receptor). The EGFR family is a group of four structurally similar growth factor receptors with tyrosine-kinase activity (EGFR, HER2/neu, Erbb3-3, Erbb4-4), which dimerize upon binding with a number of ligands, including EGF (Epidermal Growth Factor) and TGF (Transforming Growth Factor), allowing downstream transduction of mitogenic signals. Overexpression of EGFR and HER2 is frequently found in non-small-cell lung cancer (NSCLC), which accounts for over 80% of all malignant lung tumors, and has been associated with a worse clin. outcome. New agents developed to inhibit EGFR function include monoclonal antibodies and small-mol. receptor tyrosine-kinase inhibitors. In this review, results of most recent clin. trials with EGFR inhibitors including monoclonal antibodies, such as Trastuzumab (Herceptin), IMC-C225 (Cetuximab) and others (ABX-EGF, EMD 720001), and tyrosine-kinase inhibitors, such as ZD1839 (Gefitinib, Iressa), OSI-371 (Erlotinib, Tarceva) and others (CI-1033, GW2016), are summarized. In particular, final results of phase II (IDEAL 1 and 2) and III (INTACT 1 and 2) studies of ZD1839 are reported. In IDEAL trials (ZD1839 single agent in patients pre-treated with chemotherapy) there was clear evidence of tumor regression, symptoms improvement and overall clin. benefit, whereas in the two INTACT trials (ZD1839 in combination with standard platinum-based chemotherapy in chem-naive patients) ZD1839 did not improve either survival or other clin. endpoints. Possible explanations for these contradictory results and future perspectives are discussed.

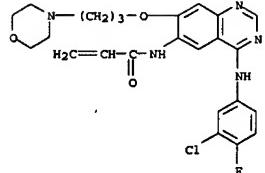
IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (epidermal growth factor receptor inhibitors in treatment of lung cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinoxolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 13 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

REFERENCE COUNT:

49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:197494 CAPLUS

DOCUMENT NUMBER: 141:23530

TITLE: Emerging roles of targeted small molecule protein-tyrosine kinase inhibitors in cancer therapy
AUTHOR(S): Smith, John K.; Mamoon, Naila M.; Duhe, Roy J.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Mississippi Medical Center, Jackson, MS, 39216-4505, USA

SOURCE: Oncology Research (2003), 14(4/5), 175-225
CODEN: ONREB; ISSN: 0965-0407

PUBLISHER: Cognizant Communication Corp.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Targeted protein-tyrosine kinase inhibitors (PTKIs) comprise a new, rapidly evolving class of mol. weight anticancer drugs. Two members of this class, imatinib (Gleevec) and gefitinib (Iressa), are currently approved for market use in the United States. This review discusses the scientific history behind these two PTKI drugs, including the role of the targeted kinase in cancer etiol., the biochem. of selective inhibition, the evaluation of clin. efficacy, and the mechanisms whereby drug resistance has emerged. Other PTKIs undergoing clin. evaluation are also described, including epidermal growth factor receptor kinase inhibitors (erlotinib, PKI166, and CI-1033) and PTKIs designed to disrupt tumor vascularization (SU5416, SU6668, SU11248, PTK787, and ZD6474). How might one apply current knowledge to the efficient development of new agents that would target as-yet-unexploited oncogenic PTKs such as chimeric anaplastic leukemia kinases or Janus kinases. Ideally, the targets should contain structurally distinct drug interaction epitopes, although it is not necessary that these epitopes be unique to a single target, because effective drugs may inhibit multiple kinases involved in an oncogenic process. Oral availability is a highly desirable feature because daily oral administration can maintain a sustained efficacious plasma concentration, whereas intermittent parenteral administration may not. Perhaps most importantly, one must verify the presence of an appropriate mol. target on a case-by-case basis before selecting a patient for PTKI therapy. Thus, the development of molecularly targeted diagnostic tools will be crucial to the ultimate success of molecularly targeted PTKI therapy.

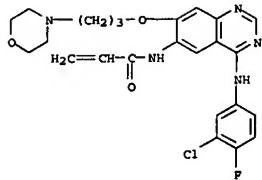
IT 289499-45-2, CI-1033

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epidermal growth factor receptor kinase inhibitor CI-1033 is designed to disrupt tumor vascularization and used in treatment of cancer therapy)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAMES)

L3 ANSWER 14 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



• 2 HCl

REFERENCE COUNT:

422 THERE ARE 422 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:182368 CAPLUS

DOCUMENT NUMBER: 140:229401

TITLE: Three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands

INVENTOR(S): Come, Jon H.; Becker, Frank; Kley, Nikolai A.; Reichel, Christoph

ATTENT ASSIGNEE(S): U.S. Pat. Appl. Publ., 238 pp., Cont.-in-part of U.S. Ser. No. 91,177.

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 2004043388 | A1 | 20040304 | US 2002-234985 | 20020903 |
| US 2003165873 | A1 | 20030904 | US 2002-91177 | 20020304 |
| PRIORITY APPLN. INFO.: | | | US 2001-272932P | P 20010302 |
| | | | US 2001-278233P | P 20010323 |
| | | | US 2001-329437P | P 20011015 |
| | | | US 2002-91177 | A2 20020304 |

AB The invention provides compns. and methods for isolating ligand-binding polypeptides for a user-specified ligand, and for isolating small mol. ligands for a user-specified target polypeptide using an improved class of hybrid ligand compds. Preparation of compds., e.g. a methotrexate moiety linked by a polyethylene glycol moiety to dexamethasone, is described.

IT 198959-99-8D, conjugates

RL: RUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN 198959-99-8 CAPLUS

CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 16 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:142967 CAPLUS

DOCUMENT NUMBER: 140:175126

TITLE: Therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies

INVENTOR(S): Elliott, William Leon; Fry, David William
PATENT ASSIGNEE(S): Warner-Lambert Company LLC, USA

SOURCE: PCT Int. Appl., 40 pp.

CODEN: PIXKD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2004014386 | A1 | 20040219 | WO 2003-IB3388 | 20030728 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JE, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MC, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SS, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, CM, KS, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AB, BY, KG, KZ, MD, RU, TJ, TM, AT, BS, BG, CR, CV, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GO, GR, ML, MR, NE, SN, TD, TG | | | | |
| US 2004067942 | A1 | 20040408 | US 2003-63281 | 20030801 |
| PRIORITY APPLN. INFO.: | | | US 2002-401705P | P 20020807 |
| | | | US 2003-462247P | P 20030411 |

AB The invention describes administration of an irreversible tyrosine kinase inhibitor such as CI-1033 in combination with one or more other antineoplastic agent(s), or ionizing radiation is synergistic for treating cancer

IT 267243-28-7

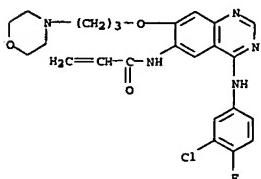
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(therapeutic combinations of erb B kinase inhibitors and antineoplastic therapies)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-

morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT:

8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L3 ANSWER 17 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:120750 CAPLUS
 DOCUMENT NUMBER: 140:175121
 TITLE: Therapeutic inhibition of protein kinases and a cellular ATP synthetic pathway in cancer cells
 INVENTOR(S): Carson, Dennis A.; Rosenbach, Michael D.; Carrera, Carlos J.; Leoni, Lorenzo M.
 PATENT ASSIGNEE(S): The Regents of the University of California, USA; Salmedix, Inc.
 SOURCE: PCT Int. Appl., 66 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2004012769 | A1 | 20040212 | WO 2003-US24439 | 20030801 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZN
RN: GH, GM, KS, LS, MW, MZ, SD, SL, SZ, T2, UG, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IS, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004096436 | A1 | 20040520 | US 2003-632592 | 20030801 |

PRIORITY APPLN. INFO.: US 2002-400568P P 20020802
 AB The present invention provides methods of treating cancer using inhibitors of protein kinases. The inhibitors of protein kinases are combined with agents that inhibit a cellular ATP synthetic pathway. Inhibitors of ATP synthesis include inhibitors of de novo purine biosynthesis, inhibitors of the salvage pathway of ATP biosynthesis, and inhibitors of the enzyme inosine monophosphate dehydrogenase.

IT 289499-45-2, CI1033
 RL: PAC (Pharmacological activity); BIOL (Biological study)
 (receptor tyrosine kinase inhibitor; therapeutic inhibition of protein kinases and cellular ATP synthetic pathway in cancer cells)
 RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quiazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

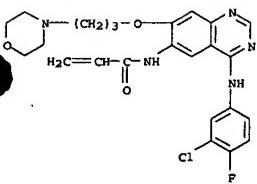
L3 ANSWER 17 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L3 ANSWER 18 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:100947 CAPLUS
 DOCUMENT NUMBER: 140:139486
 TITLE: Method of treating cancer
 INVENTOR(S): Potter, David A.
 PATENT ASSIGNEE(S): Advanced Research & Technology Institute at Indiana University, USA
 SOURCE: PCT Int. Appl., 69 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2004010937 | A2 | 20040205 | WO 2003-US23437 | 20030728 |
| WO 2004010937 | A3 | 20040405 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZN
RN: GH, GM, KS, LS, MW, MZ, SD, SL, SZ, T2, UG, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IS, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004167139 | A1 | 20040826 | US 2003-629045 | 20030728 |

PRIORITY APPLN. INFO.: US 2002-399573P P 20020726
 AB Methods for treating cancer are described here. The methods include administering to an HIV-neg. patient an m-calpain inhibitor such as ritonavir. Ritonavir or other m-calpain inhibitors can also be co-administered with other therapeutic agents such as a Cox-2 inhibitor, a taxane, or a proteasome inhibitor. Methods for determining whether a patient will respond to a particular method of treatment are also described herein.

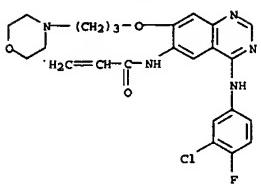
IT 289499-45-2, CI-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (treating cancer)
 RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quiazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HC1

L3 ANSWER 18 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HCl

L3 ANSWER 19 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:88605 CAPLUS

DOCUMENT NUMBER: 141:291342

TITLE: Radiosensitization by Pan ErbB Inhibitor CI-1033 in Vitro and in Vivo
AUTHOR(S): Nyati, Mukesh K.; Maheashwari, Divya; Hanasoge, Sheela; Sreekumar, Arun; Rynkiewicz, Susan D.; Chinnaian, Arul M.; Leopold, Wilbur R.; Ethier, Stephen P.; Lawrence, Theodore S.

CORPORATE SOURCE: Departments of Radiation Oncology, Ann Arbor Laboratories, Ann Arbor, MI, USA

SOURCES: Clinical Cancer Research (2004), 10(2), 691-700

CODEN: CCRP4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Overexpression of the ErbB family of receptor tyrosine kinases has been associated with uncontrolled growth of many tumor types and, therefore, presents a promising mol. target for cancer therapy. CI-1033 is a small mol. tyrosine kinase inhibitor that differs from other 4-anilinoquinazolines by being a pan ErbB (instead of epidermal growth factor receptor-specific) irreversible (instead of reversible) inhibitor. Therefore, we investigated the antitumor effect of CI-1033 alone and in combination with ionizing radiation in vitro and in vivo. We selected three human colon carcinoma cell-lines (LoVo, Caco-2, which express activated epidermal growth factor receptor and ErbB-2 family members, and SW620, which does not), and analyzed the effects of CI-1033 both in vitro and in vivo. For in vivo studies LoVo and Caco-2 cells were implanted s.c. in the flank of nude mice. After the tumor reached approx. 100 mm³, treatment was initiated with 20 mg/kg of CI-1033 (orally once daily × 5 for 3 successive weeks), radiation treatment (a total of 30 Gy given in 2 Gy once daily 5 for 3 successive weeks), or a combination of both CI-1033 and radiation treatment. We found that exposure of LoVo and Caco-2, but not SW620 cells, to CI-1033 in the range of 1-3 μM could inhibit constitutive signaling by tyrosine kinases, arrest cell growth, inhibit cells in G1, stimulate expression of p53, and induce apoptosis. The inhibition of cell growth by CI-1033 seemed to produce only minimal radiosensitization in LoVo and Caco-2 cells. In contrast, the combination of CI-1033 and radiation produced significant ($P < 0.0005$ and $P = 0.0002$, resp.) and prolonged suppression of tumor growth in both the tumor types when compared with either treatment alone. These findings suggest that CI-1033 can increase the effectiveness of radiation therapy. The extent of suppression of tyrosine kinase activity by CI-1033, rather than the amount of activity in untreated cells, seemed to be more closely associated with the efficacy of combination treatment.

IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

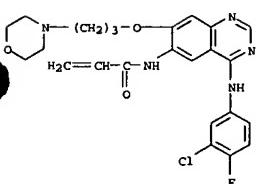
(radiosensitization by pan ErbB inhibitor CI-1033 in vitro and in vivo)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 19 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HCl

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:88574 CAPLUS

DOCUMENT NUMBER: 141:309684

TITLE: Searching for reliable epidermal growth factor receptor response predictors: Commentary re M. K. Nyati et al., Radiosensitization by Pan-ErbB inhibitor CI-1033 in vitro and in vivo. Clin. Cancer Res., 10: 691-700, 2004.

AUTHOR(S): Harari, Paul M.; Huang, Shyh-Min

CORPORATE SOURCE: Department of Human Oncology, University of Wisconsin School of Medicine and Comprehensive Cancer Center, Madison, WI, 53792, USA

SOURCE: Clinical Cancer Research (2004), 10(2), 428-432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A polemic in response to Nyati et al. Clin. Cancer. Res.: 691-700, 2004. The research of Nyati et al. (2004) entitled "Radiosensitization by pan ErbB inhibitor CI-1033 in vitro and in vivo" is reviewed with commentary and refs. Nyati et al. examined the impact of an irreversible pan ErbB tyrosine kinase inhibitor (CI-1033) across a series of colon cancer cell lines in vitro and in vivo. They suggest that the extent of suppression of tyrosine kinase activity by CI-1033, rather than the baseline activity level before treatment, may predict for ultimate treatment efficacy. They also confirm the capacity of CI-1033 to enhance radiation response (particularly in vivo) as has been identified for several other epidermal growth factor receptor (EGFR) inhibitors. Nyati et al. also suggest that selected downstream signaling mole. of the EGFR pathway may serve as candidate markers for predicting response to ErbB inhibition.

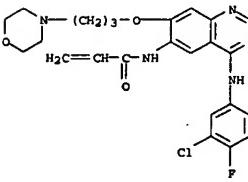
IT 289499-45-2, CI-1033

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(radiosensitization by EGFR inhibitor CI-1033: searching for reliable EGFR response predictors)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 20 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L3 ANSWER 21 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:41317 CAPLUS
 DOCUMENT NUMBER: 140:99649
 TITLE: Pharmaceutical compositions for the treatment of respiratory tract diseases comprising novel anticholinergic agents and inhibitors of EGFR-kinase
 INVENTOR(S): Pairet, Michel; Meade, Christopher John Montague; Pieper, Michael P.
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co. Kg, Germany
 SOURCE: PCT Int. Appl., 44 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|--|------------------|---|
| WO 2004004775 | A1 | 20040115 | WO 2003-EP6788 | 20030626 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, T2, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | DE 10230751 A1 20040122 DE 2002-10230751 20020709 |
| US 2004048887 | A1 | 20040311 | US 2003-614382 | 20030707 |
| PRIORITY APPLN. INFO.: | | | DE 2002-10230751 | A 20020709 |
| | | | US 2002-407746P | P 20020903 |

OTHER SOURCE(S): MARPAT 140:99649
 AB The invention relates to novel pharmaceutical compns. comprising novel anticholinergic agents and EGFR-kinase inhibitors, method for production and use thereof in the treatment of respiratory diseases. The synthesis of several EGFR-kinase inhibitors is given. Thus an inhalation capsule contained (microgram/capsule): 2,2-Diphenylpropionic acid scopoline ester methobromide 60; EGFR kinase inhibitor 3500; lactose 3440.
 IT 290301-86-9
 RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (pharmaceutical compns. for treatment of respiratory tract diseases comprising anticholinergic agents and inhibitors of EGFR-kinase)
 RN 290301-86-9 CAPLUS
 CN Glycine, N-[4-[(7-methoxy-4-[(3-methylphenyl)amino]-6-quinoxolinyl]amino)-4-oxo-2-butenyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 21 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

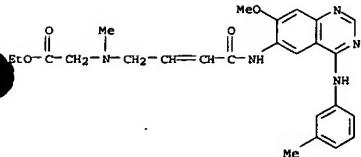
L3 ANSWER 22 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2004:41213 CAPLUS
 DOCUMENT NUMBER: 140:105249
 TITLE: Combination of mTOR inhibitor and a tyrosine kinase inhibitor for the treatment of neoplasms
 INVENTOR(S): Neel, Benjamin G.; Mohi, Golam
 PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
 SOURCE: PCT Int. Appl., 63 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|--|-----------------|---|
| WO 2004004644 | A2 | 20040115 | WO 2003-US20972 | 20030703 |
| WO 2004004644 | A3 | 20040506 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, T2, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | PRIORITY APPLN. INFO.: US 2002-394029P P 20020705
US 2002-412402P P 20020920 |

AB The invention features methods and compns. including an mTOR inhibitor and a tyrosine kinase inhibitor for reducing the proliferation of and enhancing the apoptosis of neoplastic cells. The addition of an MEK inhibitor to this combination further enhances the effectiveness of this therapeutic method.

IT 289499-45-2, Cl-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (combination of mTOR inhibitor and tyrosine kinase inhibitor for cancer therapy)

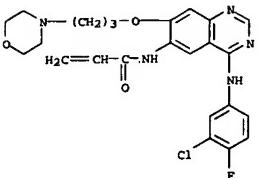
RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(4-morpholinyl)propoxy]-6-quinoxolinyl-, dihydrochloride (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HCl

L3 ANSWER 23 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:1000449 CAPLUS

DOCUMENT NUMBER: 140:35213

TITLE: CI-1033, an irreversible pan-erbB receptor inhibitor and its potential application for the treatment of breast cancer

AUTHOR(S): Allen, Lee F.; Eiseman, Irene A.; Fry, David W.; Lenehan, Peter F.

CORPORATE SOURCE: Departments of Clinical Development, Oncology and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor Laboratories, Ann Arbor, MI, USA

SOURCES: Seminars in Oncology (2003), 30(5, Suppl. 16), 65-78 CODEN: SOLGAV; ISSN: 0093-7754

PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The erbB family of cell surface receptor proteins consists of four members, all of which play a role in the development and growth of the normal breast. The activity of this signaling pathway is normally tightly controlled, and dysregulation has been shown to play a significant role in the pathogenesis and progression of breast and other cancers. The potent transforming potential of these receptors is further enhanced by the coexpression of multiple members of this receptor family, which worsens prognosis. Therapeutic blockade of erbB-2 receptor signaling has to date been shown to be effective in only a subset of chemotherapy-resistant breast cancer patients. CI-1033 is a highly potent and selective pan-erbB inhibitor that efficiently blocks signal transduction through all four members of the erbB receptor family. In addition, it covalently binds to these receptors, irreversibly inhibiting them, and thereby provides for prolonged suppression of erbB receptor-mediated signaling. Clin., it has been shown to have an acceptable side effect profile at potentially therapeutic doses and schedules. Biomarker studies have shown target inhibition in patients, and evidence of antitumor activity has also been observed in phase I studies. Given the broad expression pattern of the erbB family of receptors in solid tumors, and the important proliferative effect of co-expression of multiple erbB receptors, CI-1033, as an irreversible, pan-erbB inhibitor, has the potential to have an important role in the future treatment of breast and other cancers.

IT 289499-45-2, CI1033

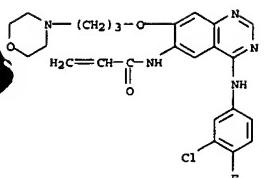
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (potential use of pan-erbB receptor inhibitor CI-1033 for treatment of breast cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAMES)

L3 ANSWER 23 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HCl

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L3 ANSWER 24 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:991359 CAPLUS

DOCUMENT NUMBER: 140:23220

TITLE: Method of treating cancer using kinase inhibitors

INVENTOR(S): Agus, David B.

PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA

SOURCE: PCT Int. Appl., 33 pp.

CODEN: PIXKD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003103676 | A2 | 20031218 | WO 2003-US17565 | 20030604 |
| WO 2003103676 | A3 | 20040325 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MC, MN, MM, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SC, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MM, MZ, SD, SL, SZ, T2, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004001833 | A1 | 20040101 | US 2003-454323 | 20030604 |

PRIORITY APPLN.: INFO.: US 2002-386622P P 20020605

AB Described herein are methods for treating cancer and other disease conditions in individuals who have either developed a resistance to conventional tyrosine kinase inhibitor (TKI) therapy or who are non-responsive as initial to conventional TKI therapy. In various embodiments, the methods include administering to a patient a resistance-surmounting quantity of a TKI on a weekly or semi-weekly basis. Alternate embodiments of the present invention include a diagnostic method for assessing an individual's probability of being resistant to TKI therapy, based upon an expression level of epithelial membrane protein-1 (EMP-1), one of the genes believed to be responsible for TKI resistance. The methods of the present invention may be particularly useful in the treatment of lung, breast, prostate, ovarian, brain and colon cancers. The methods of the present invention may be effective in blocking the HER-2 kinase domain either in addition to or in lieu of blocking the EGFR kinase domain.

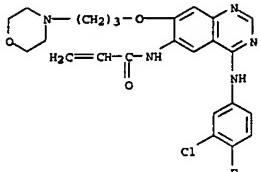
IT 289499-45-2, CI1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (assessment of cancer using inhibitors of tyrosine kinase)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-((3-chloro-4-fluorophenyl)amino)-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAMES)

L3 ANSWER 24 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



●2 HCl

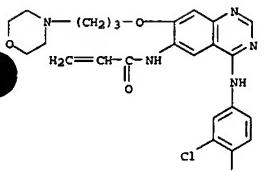
L3 ANSWER 25 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:971922 CAPLUS
 DOCUMENT NUMBER: 140:23220
 TITLE: Preventives and/or remedies for subjects with the expression or activation of her2 and/or EGFR
 INVENTOR(S): Suzuki, Tsuyoshi; Kitano, Yasunori; Yano, Shinji
 PATENT ASSIGNEE(S): Mitsubishi Pharma Corporation, Japan
 SOURCE: PCT Int. Appl., 38 pp.
 CODEN: PIXKD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2003101491 | A1 | 20031211 | WO 2003-JP6988 | 20030603 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW,
RW: GH, GM, KE, LS, MW, MZ, SD, SL, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: JP 2002-162130 A 20020603

OTHER SOURCE(S): MARPAT 140:23220
 AB Her2 and/or EGFR inhibitors to be administered to subjects with the overexpression or activation of Her2 and/or EGFR that have been subjected to an examination for detecting the expression or activity of Her2 and/or EGFR and thus regarded as having the overexpression or activation of Her and/or EGFR; and medicinal compns. containing such an inhibitor.
 IT 267243-28-7
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (quinazoline analogs as preventives and/or remedies for subjects with the expression or activation of her2 and/or EGFR)
 RN 267243-28-7 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 25 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 26 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:931201 CAPLUS
 DOCUMENT NUMBER: 140:13024
 TITLE: EGF receptor antagonists in the treatment of gastric cancer
 INVENTOR(S): Luber, Birgit; Fuchs, Margit Roswitha; Hoeffler, Heinz; Fend, Falko; Gamboa-Dominguez, Armando
 PATENT ASSIGNEE(S): Technische Universitaet Muenchen, Germany
 SOURCE: PCT Int. Appl., 153 pp.
 CODEN: PIXKD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

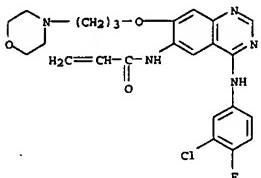
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2003097086 | A2 | 20031127 | WO 2003-EP5057 | 20030514 |
| WO 2003097086 | A3 | 20040304 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW,
RW: GH, GM, KE, LS, MW, MZ, SD, SL, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 2002-380285P P 20020515 EP 2003-4524 A 20030228

AB The invention relates to a use of (an) EGF receptor antagonist(s)/inhibitor(s) for the preparation of a pharmaceutical composition for the prevention, amelioration or treatment of gastric carcinomas, preferably for the prevention, amelioration or treatment of diffuse gastric carcinomas. Furthermore, the invention provides for a method for treating or for preventing gastric carcinomas, in particular diffuse gastric carcinomas comprising the administration of at least one EGF receptor antagonist/inhibitor to a subject in need of such a treatment or prevention.
 IT 289499-45-2, CI-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (EGF receptor antagonists in treatment of gastric cancer)
 RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 26 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HCl

L3 ANSWER 27 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:913005 CAPLUS
 DOCUMENT NUMBER: 139:391384
 TITLE: Use of inhibitors of EGFR-mediated signal transduction for the treatment of benign prostatic hyperplasia (BPH)/prostatic hypertrophy
 INVENTOR(S): Singer, Thomas; Colbatzky, Florian; Platz, Stefan
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
 SOURCE: PCT Int. Appl., 35 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003094921 | A2 | 20031120 | WO 2003-EP4606 | 20030502 |
| WO 2003094921 | A3 | 20040318 | | |
| <i>W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW</i>
<i>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG</i>
<i>DE 10221018 A1 20031127 DE 2002-10221018 20020511</i>
<i>US 2003225079 A1 20031204 US 2003-431699 20030508</i>
<i>PRIORITY APPLN. INFO.: DE 2002-10221018 A 20020511</i>
<i>US 2002-389815P P 20020618</i> | | | | |

OTHER SOURCE(S): MARPAT 139:391384

AB The invention discloses the use of EGF-receptor antagonists for the production of a medicament to prevent and/or treat benign prostatic hyperplasia and/or prostatic hypertrophy, as well as a method for the treatment or prevention of benign prostatic hyperplasia/prostatic hypertrophy involving the administration of an EGF-receptor antagonist, optionally in combination with known compds. for the treatment of benign prostatic hyperplasia/prostatic hypertrophy, and the corresponding pharmaceutical compns. Compds. of the invention include e.g. quinazoline derivs. and monoclonal antibodies. Preparation of

4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(N-(2-methoxyethyl)-N-methylamino)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline is described.

IT 439081-48-8

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

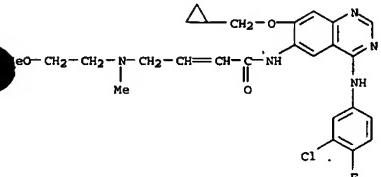
(EGFR-mediated signal transduction inhibitors for treatment of benign prostatic hyperplasia/prostatic hypertrophy)

RN 439081-48-8 CAPLUS

CN 2-Butenenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2-methoxyethyl)methylamino] (9CI) (CA INDEX NAME)

L3 ANSWER 27 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



L3 ANSWER 28 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:892616 CAPLUS
 DOCUMENT NUMBER: 139:358614
 TITLE: Methods for the treatment of glaucoma and other conditions mediated by NOS-2 expression via inhibition of the EGFR pathway
 INVENTOR(S): Liu, Bin; Neufeld, Arthur H.
 PATENT ASSIGNEE(S): Washington University, USA
 SOURCE: PCT Int. Appl., 52 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003092693 | A1 | 20031113 | WO 2003-US14484 | 20030506 |
| <i>W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW</i>
<i>RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG</i>
<i>US 2003232741 A1 20031218 US 2003-430527 20030506</i>
<i>PRIORITY APPLN. INFO.: US 2002-378254P P 20020506</i> | | | | |

AB Therapeutic methods and compns. for the treatment of glaucoma and other conditions mediated at least in part by the expression of NOS-2 are provided.

IT 289499-45-2, CI-1033

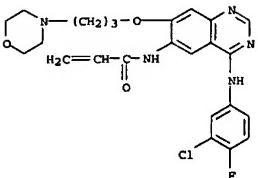
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (methods for treatment of glaucoma and other conditions mediated by NOS-2 expression via inhibition of EGFR pathway)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HCl

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 29 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:855936 CAPLUS

DOCUMENT NUMBER: 139:350749

TITLE: Preparation of 4-aminoquinazolines as inhibitors of

epidermal growth factor receptor (EGFR)
Himmelbach, Frank; Jung, Birgit; Solca, Flavio
Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.,

Germany

SOURCE: PCT Int. Appl., 56 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

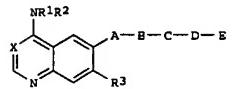
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2003089439 | A1 | 20031030 | WO 2003-EP38282 | 20030414 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10217689 | A1 | 20031113 | DE 2002-10217689 | 20020419 |
| US 2004044014 | A1 | 20040304 | US 2003-417647 | 20030417 |
| PRIORITY APPLN. INFO.: | | | DE 2002-10217689 | A 20020419 |
| | | | US 2002-387021P | P 20020607 |

OTHER SOURCE(S): MARPAT 139:350749

GI

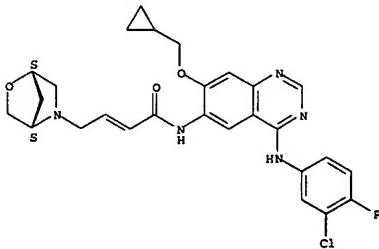


AB Title compds. [I; R1 = H, alkyl; R2 = Ph, benzyl, 1-phenylethyl in which Ph is substituted; R3 = H, F, Cl, Br, OH, alkoxy, fluorinated OMe, OEt, substituted alkoxy; cycloalkyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, etc.; A = imino, alkylimino, B = CO, SO2; C = (substituted) 1,3-allenylene, 1,1-vinylene, 1,2-vinylene, C=CH, etc.; D = (branched) alkylene; E = bridged pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl] tautomers, stereoisomers, mixts. and salts thereof, particularly their physiol. compatible salts with inorg. or organic acids, were prepared. Thus, a solution of LiCl in H2O was treated with 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-1-oxo-2-but-en-1-yl)amino]-7-[(6-tetrahydrofuran-3-yl)oxy]quinazoline. The latter inhibited EGFR-receptor kinase with IC50 = 0.5 nM. The invention also relates to the use of these compds. for treating diseases, particularly tumor diseases and benign prostatic hyperplasia (BPH), diseases of the lungs and of the respiratory tract.

L3 ANSWER 29 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
[2-(diethoxyphosphoryl)acetyl]amino-7-((S)-(tetrahydrofuran-3-yl)oxy)quinazoline (prep. given) in THF followed by addn. of KOH-pellets and cooling at -3°. Then, the reaction mixt. was dropwise treated with (1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)acetalddehyde hydrochloride (prep. given) for 5 min at 0° followed by stirring for 10 min at 0° and for 20 min at room temp. to give 60% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl]-1-oxo-2-but-en-1-yl)amino]-7-[(6-tetrahydrofuran-3-yl)oxy]quinazoline. The latter inhibited EGFR-receptor kinase with IC50 = 0.5 nM. The invention also relates to the use of these compds. for treating diseases, particularly tumor diseases and benign prostatic hyperplasia (BPH), diseases of the lungs and of the respiratory tract.

IT 618061-81-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

RN 618061-81-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl- (9CI) (CA INDEX NAME)Absolute stereochemistry.
Double bond geometry unknown.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 30 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:656610 CAPLUS

DOCUMENT NUMBER: 139:202486

TITLE: Inhalants containing anticholinergic agents and EGFR kinase inhibitors

INVENTOR(S): Jung, Birgit; Pairet, Michel; Pieper, Michael P.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G.,

Germany

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2003068264 | A1 | 20030821 | WO 2003-EP1357 | 20030212 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10206505 | A1 | 20030828 | DE 2002-10206505 | 20020216 |
| US 2003158196 | A1 | 20030921 | US 2003-360064 | 20030207 |
| EP 1478398 | A1 | 20041124 | EP 2003-704593 | 20030212 |
| PRIORITY APPLN. INFO.: | | | | |
| R: AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, PL, RO, MK, CY, AL, IR, BG, CZ, BE, HU, SK | | | DE 2002-10206505 | A 20020216 |
| | | | US 2002-369213P | P 20020401 |
| | | | WO 2003-EP1357 | W 20030212 |

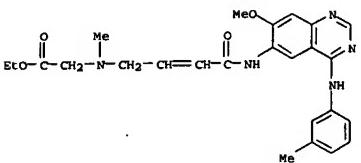
AB The invention relates to novel medicinal compds. on the basis of anticholinergic agents and EGFR kinase inhibitors, methods for their production and their use for treating respiratory diseases. Thus a series of quinazoline derivs. were synthesized that were EGFR kinase inhibitors. A typical inhalation powder contained (mg/capsule): tiotropium bromide 10.8; EGFR kinase inhibitor 3500; lactose 3469.2.

IT 290301-86-9P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhalants containing anticholinergic agent and EGFR kinase inhibitors)

RN 290301-86-9 CAPLUS
CN Glycine, N-[4-[(7-methoxy-4-[(3-methylphenyl)amino]-6-quinazolinyl)amino]-4-oxo-2-but enyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 30 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN

(Continued)



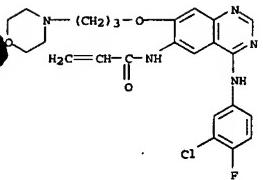
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:633416 CAPIUS
 DOCUMENT NUMBER: 139:173786
 TITLE: Method for treating diseases associated with abnormal kinase activity
 INVENTOR(S): Lyons, John; Rubinfeld, Joseph
 PATENT ASSIGNEE(S): Supergen, Inc., USA
 SOURCE: PCT Int. Appl., 64 pp.
 CODEN: PIXKD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------------|-----------------|-------------|
| WO 2003065995 | A2 | 20030814 | WO 2003-US3537 | 20030206 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MM, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, T2, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TZ | | | | |
| US 2003147813 | A1 | 20030807 | US 2002-71849 | 20020207 |
| US 2004127453 | A1 | 20040701 | US 2002-206854 | 20020726 |
| PRIORITY APPLN. INFO.: | | US 2002-71849 | | A1 20020207 |
| | | US 2002-206854 | | A1 20020726 |
| AB Methods are provided for treating diseases associated with abnormal activity of kinases such as chronic myelogenous leukemia. The method comprises: administering a DNA methylation inhibitor to the patient in therapeutically effective amount; and administering a kinase inhibitor such as imatinib mesylate to the patient in therapeutically effective amount, such that the in vivo activity of the kinase is reduced relative to that prior to the treatment. The method can be used to treat cancer associated with abnormal activity of kinases such as phosphatidylinositol 3'-kinase (PI3K), protein kinases including serine/threonine kinases such as Raf kinases, protein kinase kinases such as MEK, and tyrosine kinases such as those in the epidermal growth factor receptor family (EGFR), platelet-derived growth factor receptor family (PDGFR), vascular endothelial growth factor receptor (VEGFR) family, nerve growth factor receptor family (NGFR), fibroblast growth factor receptor family (FGFR) insulin receptor family, ephrin receptor family, Met family, Ror family, c-kit family, Src family, JAK family, Fak family, Btk family, Syk/ZAP-70 family, and Abl family. | | | | |
| IT 289499-45-2, C1033
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of diseases associated with abnormal tyrosine kinase activity with tyrosine kinase inhibitor and DNA methylation inhibitor) | | | | |
| RN 289499-45-2 CAPIUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinalinyl]-, dihydrochloride (9CI) (CA INDEX NAME) | | | | |

L3 ANSWER 31 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN

(Continued)



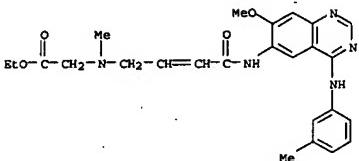
● 2 HCl

L3 ANSWER 32 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:607455 CAPIUS
 DOCUMENT NUMBER: 139:159940
 TITLE: Use of tyrosine kinase inhibitors for treatment of pulmonary inflammatory conditions
 INVENTOR(S): Jung, Birgit; Puschner, Hubert
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma G.m.b.H. & Co. K.-G., Germany
 SOURCE: Ger. Offen., 24 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|------------------|------------------|-------------|
| DE 10204462 | A1 | 20030807 | DE 2002-10204462 | 20020205 |
| WO 2003066060 | A2 | 20030814 | WO 2003-EP814 | 20030128 |
| WO 2003066060 | A3 | 20040115 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MM, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: CH, GM, KS, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TZ | | | | |
| EP 1474149 | A2 | 20041110 | EP 2003-704474 | 20030128 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, IR, BG, CZ, BE, RU, HU | | | | |
| US 2003149062 | A1 | 20030807 | US 2003-353616 | 20030129 |
| PRIORITY APPLN. INFO.: | | DE 2002-10204462 | | A 20020205 |
| | | WO 2003-EP814 | | WO 20030128 |
| OTHER SOURCE(S): MARPAT 139:159940
AB The invention discloses the use of quinazoline deriva. (Markush included), or the corresp. (1) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-dimethylaminocyclohexyl)amino]pyrimido[5,4-d]pyrimidine; (2) 4-[(R)-1-(4-hydroxyphenyl)amino]-6-(4-hydroxyphenyl)-1H-pyrido[2,3-d]pyrimidine; (3) 4-[(3-Chloro-4-(3-fluoro-4-benzoyloxy)phenyl)amino]-6-[5-((3-methacryloyl)butyl)amino]methyl]-furan-2-yl)quinazoline; or the antibody cetuximab, ABX-EGF, Mab ICR-62 and EGFR antisense, their tautomers, their stereoisomers and their salts, in particular their physiol. compatible salts with inorg. or organic acids or bases for the production of a medicament for prevention or treatment of diseases of the respiratory system or the lung. Preparation of quinazoline compounds is included. | | | | |
| IT 290301-86-9
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PRSP (Preparation); USES (Uses)
(tyrosine kinase inhibitors for treatment of pulmonary inflammatory conditions) | | | | |
| RN 290301-86-9 CAPIUS
CN Glycine, N-[4-[(7-methoxy-4-[(3-methylphenyl)amino]-6-quinalinyl]amino)-4-oxo-2-but enyl]-N-methyl-, ethyl ester (9CI) (CA INDEX NAME) | | | | |

L3 ANSWER 32 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



L3 ANSWER 33 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:355612 CAPLUS
 DOCUMENT NUMBER: 138:362649
 TITLE: Treatment of cancer with anti-ErbB2 antibodies
 INVENTOR(S): Sliwkowski, Mark X.
 PATENT ASSIGNEE(S): Genentech, Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of U.S. Ser. No. 602,812.
 CODEN: USXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

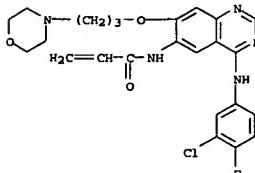
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|------|----------|-----------------|-------------|
| US 2003086924 | A1 | 20030508 | US 2002-268501 | 20021010 |
| US 2004013667 | A1 | 20040122 | US 2003-608626 | 20030627 |
| PRIORITY APPLN. INFO.: | | | US 1999-141316P | P 19990625 |
| | | | US 2000-602812 | A2 20000623 |
| | | | US 2002-268501 | A2 20021010 |

AB The present application describes methods for treating cancer with anti-ErbB2 antibodies, such as anti-ErbB2 antibodies that block ligand activation of an ErbB receptor. Recombinant humanized monoclonal antibody 2C4 was effective in inhibiting breast cancer tumor growth in MCF7 xenografts.

IT 289499-45-2, CI-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as tyrosine kinase inhibitor in combination with anti-ErbB2 antibodies; cancer treatment with anti-ErbB2 antibodies)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(4-morpholinyl)propoxy]-6-quinazolinyl-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L3 ANSWER 33 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)

L3 ANSWER 34 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:300894 CAPLUS
 DOCUMENT NUMBER: 138:297633
 TITLE: Method of treatment of thyroid cancer
 INVENTOR(S): Fagin, James Alexander
 PATENT ASSIGNEE(S): The University of Cincinnati, USA
 SOURCE: PCT Int. Appl., 20 pp.
 CODEN: PIXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2003030908 | A2 | 20030417 | WO 2002-US32195 | 20021008 |
| WO 2003030908 | A3 | 20031106 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KR, IS, MW, MZ, SD, SL, SZ, TZ, UC, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, PR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 2002-778482 A2 20040714 EP 2002-778482 20021008 | | | | |
| R: AT, BB, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IB, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| US 2004191254 A1 20040930 US 2004-491859 20040407 | | | | |
| US 2001-327880 P 20011009 | | | | |
| WO 2003-US32195 W 20021008 | | | | |

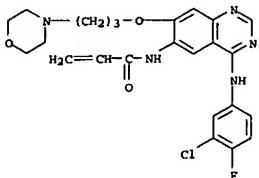
PRIORITY APPLN. INFO.:
 AB The invention relates to a method of treating a warm-blooded animal, especially a human, having a disease which is mediated or characterized by mutations in the RET gene, or thyroid cancer, especially thyroid cancer harboring RET mutations, comprising administering to said animal a therapeutically effective amount of a compound which decreases the activity of the epidermal growth factor (EGF), especially a compound as defined herein.

IT 289499-45-2, CI-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (treatment of thyroid cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(4-morpholinyl)propoxy]-6-quinazolinyl-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 34 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)



●2 HCl

L3 ANSWER 35 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2003:154278 CAPIUS
 DOCUMENT NUMBER: 138:198670
 TITLE: GnRH agonist combination drugs
 INVENTOR(S): Furuya, Shuichi; Kusaka, Masami
 PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
 SOURCE: PCT Int. Appl., 73 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|---------------------------|
| WO 2003015820 | A1 | 20030227 | WO 2002-JP8130 | 20020808 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, ES, FI, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2003137814 | A2 | 20030514 | JP 2002-231922 | 20020808 |
| EP 1424080 | A1 | 20040602 | EP 2002-758814 | 20020808 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| PRIORITY APPLN. INFO.: JP 2001-244616 | | | | A 20010810 |
| | | | | WO 2002-JP8130 W 20020808 |

AB In the field of pharmaceuticals, it is intended to provide drugs whereby the preventive and therapeutic effects of a GnRH agonist on various diseases can be enhanced and QOL can be improved. More specifically, combination drugs characterized in that the GnRH agonist is combined with a chemical selected from among SERM, SARM, sex hormone synthesis inhibitors, receptor-type tyrosine kinase inhibitors, bone metabolism regulators, drugs for immunotherapy, cytokine/chemokine inhibitors and endothelin receptor antagonists. Owing to these combinations, excellent effects of enhancing the preventive and therapeutic effects of the GnRH agonist on various diseases and relieving side effects can be established. Furthermore, QOL can be improved thereby.

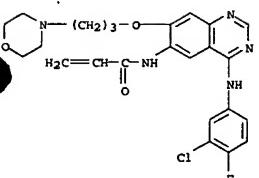
IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (GnRH agonist combination drugs for treating various diseases and relieving side effects)

RN 289499-45-2 CAPIUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 35 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)



●2 HCl

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 36 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:8967 CAPIUS
 DOCUMENT NUMBER: 139:62338
 TITLE: Small molecule tyrosine kinase inhibitors: clinical development of anticancer agents
 AUTHOR(S): Laird, A. Douglas; Cherrington, Julie M.
 CORPORATE SOURCE: SUGEN Inc., South San Francisco, CA, 94080, USA
 SOURCE: Expert Opinion on Investigational Drugs (2003), 12(1), 51-64
 CODEN: SOIDER; ISSN: 1354-3784

PUBLISHER: Ashley Publications Ltd.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

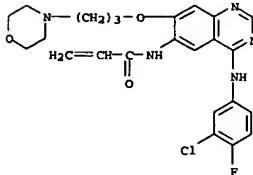
AB A review. Numerous small mol. synthetic tyrosine kinase inhibitors are in clin. development for the treatment of human cancers. These fall into three broad categories: inhibitors of the epidermal growth factor receptor tyrosine kinase family (e.g., Iressa and Tarceva), inhibitors of the split kinase domain receptor tyrosine kinase subgroup (e.g., PTK787/ZK 222584 and SU11248) and inhibitors of tyrosine kinases from multiple subgroups (e.g., Gleevec). In addition, agents targeting other tyrosine kinases implicated in cancer, such as Met, Tie-2 and Src, are in preclin. development. As experience is gained in the clinic, it has become clear that unleashing the full therapeutic potential of tyrosine kinase inhibitors will require patient preselection, better assays to guide dose selection, knowledge of mechanism-based side effects and ways to predict and overcome drug resistance.

IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (small mol. tyrosine kinase inhibitors and clin. development of anticancer agents)

RN 289499-45-2 CAPIUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 37 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:974164 CAPLUS
 DOCUMENT NUMBER: 139:143003
 TITLE: Clinical evaluation of agents targeting epidermal growth factor receptor (EGFR) in cancer
 AUTHOR(S): Lin, Edward H.; Abruzzese, James L.
 CORPORATE SOURCE: Department of Gastrointestinal Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
 SOURCE: Oncogene-Directed Therapies (2003), 313-330.
 Editor(s): Rak, Janusz. Humana Press Inc.: Totowa, N.J.
 CODEN: 69DKTX; ISBN: 0-89603-982-X
 DOCUMENT TYPE: Conference; General Review
 LANGUAGE: English

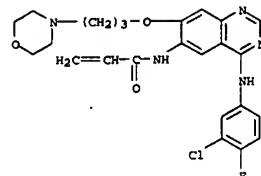
AB A review. Proteins encoded by oncogenes and tumor-suppressor genes are the essential signaling components of the complex cellular signaling networks. Cancer arises from a multi-step process promoted by the imbalanced growth signals as a consequence of gain of oncogenes and/or loss of tumor suppressor genes. The six essential cancer hallmarks include persistent cell growth signals, insensitivity to anti-growth signals, evasion of apoptosis, persistent angiogenesis, gain of cell immortality, and tumor invasion and metastasis. As an oncogene, gain of epidermal growth factor receptor (EGFR) function is achieved through EGFR over-expression and has been shown to be associated with almost all the six essential hallmarks of cancer except the gain of cell immortality. In various exptl. models, EGFR inhibition leads to regression of tumor cell growth, inhibition of angiogenesis, induction of apoptosis, and inhibition of tumor invasion and metastasis. Furthermore, over-expression of EGFR, frequently observed in a number of human cancers, is associated with poor overall prognosis, increased tumor recurrence, and decreased patient survival.

The hypothesis that EGFR might be a cancer therapeutic target was proposed by Mendelsohn in the early 1980s; emerging only recently are the promising clin. trial results from a number of EGFR antagonists in different human cancers. This review will discuss the clin. developments and future directions of EGFR antagonists in cancer treatment.

IT 289499-45-2, CI-1033
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses); (clin. evaluation of agents targeting epidermal growth factor receptor (EGFR) in cancer)

RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl], dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 37 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

REFERENCE COUNT: 135 THERE ARE 135 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

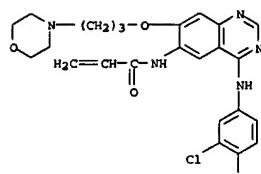
L3 ANSWER 38 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:651435 CAPLUS
 DOCUMENT NUMBER: 138:180074
 TITLE: Potential benefits of the irreversible pan-erbB inhibitor, CI-1033, in the treatment of breast cancer
 AUTHOR(S): Allen, Lee F.; Lenehan, Peter F.; Eiseman, Irene A.; Elliott, William L.; Fry, David W.
 CORPORATE SOURCE: Departments of Clinical Development, Oncology, and Cancer Pharmacology, Pfizer Global Research and Development, Ann Arbor, MI, USA
 SOURCE: Seminars in Oncology (2002), 29(3, Suppl. 11), 11-21
 PUBLISHER: W. B. Saunders Co.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review. Transmembrane receptor Tyr kinases were shown to play an important role in the modulation of growth factor signaling and regulation of key cellular processes. The erbB receptor family is part of the receptor Tyr kinase superfamily and consists of 4 members, erbB-1, erbB-2, erbB-3, and erbB-4. A majority of solid tumors express 1 or more members of this receptor family, and coexpression of multiple erbB receptors leads to an enhanced transforming potential and worsened prognosis. The erbB receptor family was shown to play an important role in both the development of the normal breast and in the pathogenesis and progression of breast cancer. Receptor overexpression was also shown to be a neg. prognostic indicator and to correlate with both tumor invasiveness and a lack of responsiveness to standard treatment. Clin. blockade of the erbB-2 receptor has recently been shown to provide benefit in a subset of chemotherapy-resistant breast cancer patients. CI-1033 is an orally available pan-erbB receptor Tyr kinase inhibitor that, unlike the majority of receptor inhibitors, effectively blocks signal transduction through all 4 members of the erbB family. In addition, it blocks the highly tumorigenic, constitutively activated variant of erbB-1, EGFRvIII, and inhibits downstream signaling through both the Ras/MAP kinase, and PI-3 kinase/AKT pathways. CI-1033 is also unique in that it is an irreversible inhibitor, thereby providing prolonged suppression of erbB receptor-mediated signaling. Preclin. data have shown CI-1033 to be efficacious against a variety of human tumors in mouse xenograft models, including breast carcinomas. In a phase I study, CI-1033 was shown to have an acceptable side effect profile at potentially therapeutic dose levels and demonstrates evidence of target biomarker modulation. Antitumor activity was also observed in this study, including 1 partial clin. response and stable disease in over 30% of patients, including 1 patient with heavily pretreated breast cancer. By virtue of its pan-erbB receptor inhibition and potent interruption of downstream mitogenic signaling pathways, CI-1033 may have clin. activity for solid tumors that overexpress 1 erbB family member, coexpress multiple members of the erbB family, or express a constitutively activated, mutated form of these receptors. Given the important role of the erbB receptor family in the pathogenesis and progression of breast cancer, an irreversible pan-erbB inhibitor like CI-1033 could have an important role to play in the future treatment of breast cancer.

IT 289499-45-2 CI-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses); (CI-1033 in treatment of breast cancer)

RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl], dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 38 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



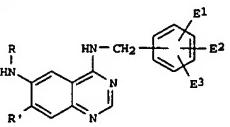
● 2 HCl

REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L3 ANSWER 39 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:610316 CAPLUS
 DOCUMENT NUMBER: 137:163829
 TITLE: Use of a composition comprising a retinoid and an Erb inhibitor in the preparation of a medicament for the treatment of retinoid skin damage
 INVENTOR(S): Elder, James Tilford; Varani, James
 PATENT ASSIGNEE(S): Warner-Lambert Company, USA
 SOURCE: Eur. Pat. Appl., 43 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| EP 1230919 | A2 | 20020814 | EP 2002-2611 | 20020205 |
| EP 1230919 | A3 | 20021218 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, | | | | |
| NZ 516873 | A | 20031128 | NZ 2002-516873 | 20020128 |
| CA 2370236 | AA | 20020812 | CA 2002-2370236 | 20020131 |
| AU 2002015470 | A5 | 20020815 | AU 2002-15470 | 20020207 |
| CN 1370535 | A | 20020925 | CN 2002-104570 | 20020208 |
| US 2002169176 | A1 | 20021114 | US 2002-73569 | 20020211 |
| ZA 2002001157 | A | 20030811 | ZA 2002-1157 | 20020211 |
| JP 2002275095 | A2 | 20020925 | JP 2002-33608 | 20020212 |
| US 2004198752 | A1 | 20041007 | US 2004-824182 | 20040414 |
| PRIORITY APPLN. INFO.: | | | US 2001-266220P | P 20010212 |
| | | | US 2002-73569 | A1 20020211 |

OTHER SOURCE(S): MARPAT 137:163829
 GI



I

AB Erb inhibitors used in combination with retinoids are effective to prevent skin injury otherwise caused by retinoids alone. A method of treating skin aging and similar skin disorders comprises administering retinoids in combination with erb inhibitors I (E1-E3 include halo; R is alkylcarbonyl or alkenylcarbonyl; R' is lower alkoxy optionally substituted with amino groups).

IT 198959-99-8

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(retinoid and Erb inhibitor for treatment of retinoid skin damage)

L3 ANSWER 40 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:604225 CAPLUS
 DOCUMENT NUMBER: 138:162767
 TITLE: EGF signal transduction and its molecular targeted drugs against cancer
 AUTHOR(S): Sone, Saburo; Yamamoto, Akihiko
 CORPORATE SOURCE: Dep. Internal Med. Molecular Therapeutics, Univ. Tokushima Sch. Med., Japan
 SOURCE: Saishin Igaku (2002), 57(7), 1712-1717
 PUBLISHER: Saishin Igakusha
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: Japanese
 AB A review. The epidermal growth factor receptor (EGFR) and its inhibition in cancer therapy is reviewed together with the mechanism related to EGF signal transduction of antitumor agents such as EGFR antibody (C225) and EGFR tyrosine kinase inhibitors (ZD1839, OSI-774, and CI-1033).

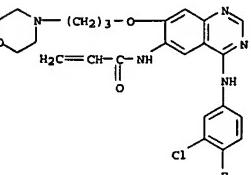
IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(EGF signal transduction and its mol. targeted drugs against cancer)

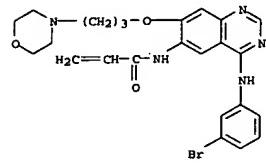
RN 289499-45-2 CAPLUS

CN 2-Propanamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxyl]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L3 ANSWER 39 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 ACCESSION NUMBER: 198959-99-8 CAPLUS
 DOCUMENT NUMBER: 2-Propanamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



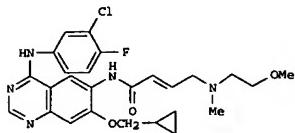
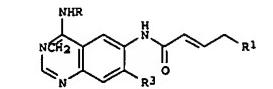
L3 ANSWER 41 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:487536 CAPLUS
 DOCUMENT NUMBER: 137:63250
 TITLE: Quinazoline derivatives as inhibitors of human EGFR tyrosine kinase
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Blech, Stefan; Jung, Birgit; Baum, Elke; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
 SOURCE: PCT Int. Appl., 64 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2002050043 | A1 | 20020627 | WO 2001-EPI4569 | 20011222 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, C2, D5, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MA, MD, MC, MK, MM, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZB, AZ, BY, KG, KZ, MD, RU, TR, TZ, TN, RW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CV, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10063435 | A1 | 20020704 | DE 2000-10063435 | 20001220 |
| CA 2432428 | AA | 20020627 | CA 2001-2432428 | 20011212 |
| AU 2002019174 | AS | 20020701 | AU 2002-19174 | 20011212 |
| EP 1345910 | A1 | 20030924 | EP 2001-271363 | 20011212 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, | | | | |
| EE 20030300 | A | 20031015 | EE 2003-300 | 20011212 |
| BR 2001016266 | A | 20040217 | BR 2001-16266 | 20011212 |
| JP 2004516283 | T2 | 20040603 | JP 2002-551540 | 20011212 |
| US 2002173509 | A1 | 20021121 | US 2001-23099 | 20011217 |
| ZA 2003004141 | A | 20040415 | ZA 2003-4141 | 20030528 |
| NO 2003002726 | A | 20030616 | NO 2003-2726 | 20030616 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10063435 | A 20001220 |
| | | | US 2000-259201P | P 20001228 |
| | | | WO 2001-EPI4569 | W 20011212 |

OTHER SOURCE(S): MARPAT 137:63250
 GI

L3 ANSWER 41 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



AB Quinazoline derivs. I [R = PhCH₂, PhCHMe, 3,4-CI(F)C₆H₃, R1 = NMe₂, NEt₂, NEtCH₂CH₂OMe, N(CH₂CH₂OMe)₂, morpholino; R2 = Me, Et, CHMe₂, cyclopropyl, CH₂CH₂OMe, 3-tetrahydrofuryl, 2-tetrahydrofurylmethyl; R3 = cyclopropylmethoxy, cyclobutoxy, cyclopentyloxy, 3-tetrahydrofuranylmethoxy, 2-tetrahydrofuranylmethoxy, 3-tetrahydrofuranylmethoxy, 4-tetrahydrofuranylmethoxy, 4-tetrahydrofuranylmethoxy] were prepared for use as inhibitors of signal transduction caused by human EGFR receptor tyrosine kinase. They are useful in the treatment of tumoral diseases, diseases of the lung and the respiratory tract, the gastrointestinal tract, and the gallbladder and bile ducts. Thus, the quinazoline II was prepared by converting bromocrotonic acid to its chloride, and reaction with 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline, followed by MeNHCH₂CH₂OMe. II had an IC₅₀ against human EGFR receptor kinase of 0.7 nM.

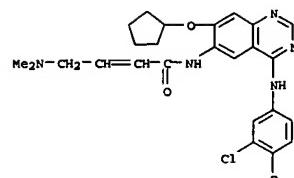
IT 439081-10-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of quinazoline derivs. as inhibitors of human EGFR tyrosine kinase)

RN 439081-10-4 CAPLUS**CN** 2-Butenanide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-(dimethylamino)-(9CI) (CA INDEX NAME)

L3 ANSWER 41 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT:

10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 42 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:414301 CAPLUS

DOCUMENT NUMBER: 138:32893

TITLE: Drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases: implications for cancer therapy

AUTHOR(S): Citri, Ami; Alroy, Iris; Lavi, Sarit; Rubin, Chanan; Xu, Wanping; Grammatikakis, Nicolas; Patterson, Cam; Necker, Len; Fry, David W.; Yarden, Yosef

CORPORATE SOURCE: Department of Biological Regulation, The Weizmann Institute of Science, Rehovot, 76100, Israel

SOURCE: EMBO Journal (2002), 21(10), 2407-2417

CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Overexpression of ErbB-2/HER2 is associated with aggressive human malignancies, and therapeutic strategies targeting the oncoprotein are currently in different stages of clin. application. Tyrosine kinase inhibitors (TKIs) that block the nucleotide-binding site of the kinase are especially effective against tumors. Here the authors report an unexpected activity of TKIs: along with inhibition of tyrosine phosphorylation, they enhance ubiquitylation and accelerate endocytosis and subsequent intracellular destruction of ErbB-2 mols. Especially potent is an irreversible TKI (CI-1033) that alkylates a cysteine specific to ErbB receptors. The degradative pathway stimulated by TKIs appears to be chaperone mediated, and is common to the heat shock protein 90 (Hsp90) antagonist geldanamycin and a stress-induced mechanism. In agreement with this conclusion, CI-1033 and geldanamycin additively inhibit tumor cell growth. Based upon a model for drug-induced degradation of ErbB-2, the authors propose a general strategy for selective destruction of oncoproteins by targeting their interaction with mol. chaperones.

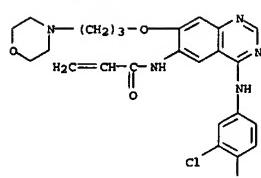
IT 289499-45-2, CI-1033

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(drug-induced ubiquitylation and degradation of ErbB receptor tyrosine kinases and implications for cancer therapy with tyrosine kinase inhibitors and Hsp90 antagonist geldanamycin)

RN 289499-45-2 CAPLUS**CN** 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(3-(4-morpholinyl)propoxy)-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 42 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

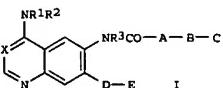
REFERENCE COUNT:

32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 43 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:171892 CAPLUS
 DOCUMENT NUMBER: 136:216762
 TITLE: Preparation of 4-amino-6-heterocyclycarbonylaminouinazolines as epidermal growth factor receptor signal transduction inhibitors
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit;
 Blech, Stefan; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
 SOURCE: PCT Int. Appl., 53 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2002018376 | A1 | 20020307 | WO 2001-EP9536 | 20010818 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10042062 | A1 | 20020307 | DE 2000-10042062 | 20000826 |
| AU 2001095482 | A5 | 20020313 | AU 2001-95482 | 20010818 |
| CA 2417907 | AA | 20030130 | CA 2001-2417907 | 20010818 |
| EP 1315720 | A1 | 20030604 | EP 2001-976108 | 20010818 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004057538 | T2 | 20040311 | JP 2002-523891 | 20010818 |
| US 2002115675 | A1 | 20020822 | US 2001-934631 | 20010822 |
| US 6740651 | B2 | 20040525 | | |
| PRIORITY APPLN. INFO.: | | | DE 2000-10042062 | A 20000826 |
| | | | US 2000-230542P | P 20000905 |
| | | | WO 2001-EP9536 | W 20010818 |

OTHER SOURCE(S): MARPAT 136:216762
 GI

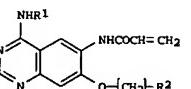


AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = (substituted) alkenyl, alkenylcarbonyl, etc.; C = (substituted) 2-oxomorpholin-4-yl, etc; D =

L3 ANSWER 44 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:171891 CAPLUS
 DOCUMENT NUMBER: 136:216761
 TITLE: Preparation of 4-amino-6-vinylcarbonylaminouinazoline as epidermal growth factor receptor signal transduction inhibitors
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit;
 Blech, Stefan; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
 SOURCE: PCT Int. Appl., 52 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2002018375 | A1 | 20020307 | WO 2001-EP9534 | 20010818 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10042064 | A1 | 20020307 | DE 2000-10042064 | 20000826 |
| AU 2002010444 | A5 | 20020313 | AU 2002-10444 | 20010818 |
| CA 2417955 | AA | 20030130 | CA 2001-2417955 | 20010818 |
| EP 1322645 | A2 | 20030702 | EP 2001-978279 | 20010818 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004057537 | T2 | 20040311 | JP 2002-523890 | 20010818 |
| US 6403580 | B1 | 20020611 | US 2001-935498 | 20010823 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10042064 | A 20000826 |
| | | | US 2000-230541P | P 20000905 |
| | | | WO 2001-EP9534 | W 20010818 |

OTHER SOURCE(S): MARPAT 136:216761
 GI

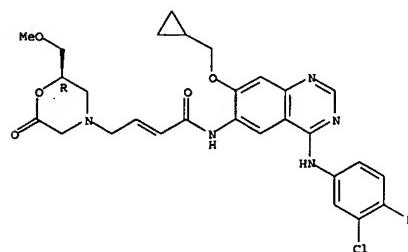


AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-(2-oxotetrahydrofuran-4-yl)methylamino, N(CH2CO2R)2, (substituted) R4COCH2CH2CH2OH, 2-oxomorpholin-4-yl; R3 = H, Me, Et; R4 = H, alkyl; n = 2-4], were prepared. Thus, a mixture of CH2:CHCO2H and Et3N was stirred for 1 h at -50° with CH2:CHCO2H in THF followed by addition of 6-amino-4-((3-chloro-4-yl)propoxy)quinazoline (preparation given) in THF at -55° and slowly heating up to 0° up to completely conversion

L3 ANSWER 43 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 oxalkenyl, O; B = (substituted) amino, alkenylimino, imidazolyl, cycloalkyl; or DE = H, (substituted) alkoxy, etc.), were prepd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-N-(ethoxycarbonylmethyl)-N-(R)-2-hydroxy-3-methoxypropyl)amino]-1-oxo-2-buten-1-ylamino-7-cyclopropylmethoxyquinazoline (prepn. given) and MeSO2OH in MeCN were stirred for 1 h under reflux to give 69% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(R)-2-methoxymethyl]-6-oxomorpholin-4-yl)-1-oxo-2-buten-1-ylamino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC50 = 2 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT 402569-98-6P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of (amino)(heterocyclycarbonylaminooquinazolines as epidermal growth factor receptor signal transduction inhibitors)
 RN 402569-98-6 CAPLUS
 CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2R)-2-(methoxymethyl)-6-oxo-4-morpholinyl] (9CI) (CA INDEX NAME)

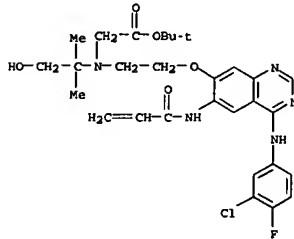
Absolute stereochemistry.
 Double bond geometry unknown.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 44 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 oxomorpholin-4-yl)propoxy)-6-[(vinylcarbonyl)amino]quinazoline. One of the exemplified examples, 4-[(R)-1-phenylethyl)amino]-7-(2,2-dimethyl-6-oxomorpholin-4-yl)ethoxy-6-[(vinylcarbonyl)amino]quinazoline, inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC50 = 0.4 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT 402724-13-4P
 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (preparation of (amino)(vinylcarbonylaminooquinazolines as epidermal growth factor receptor signal transduction inhibitors)
 RN 402724-13-4 CAPLUS
 CN Glycine, N-[2-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxyethyl-N-(2-hydroxy-1,1-dimethylethyl)-1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

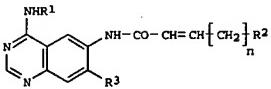


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 45 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:171889 CAPLUS
 DOCUMENT NUMBER: 136:232315
 TITLE: Preparation of 4-amino-6-vinylcarbonylaminoquinazoline s as epidermal growth factor receptor signal transduction inhibitors
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit;
 Blech, Stefan; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
 SOURCE: PCT Int. Appl., 78 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2002018373 | A1 | 20020307 | WO 2001-EP9537 | 20010818 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10042060 | A1 | 20020307 | DE 2000-10042060 | 20000826 |
| US 2002077330 | A1 | 20020620 | US 2001-929931 | 20010815 |
| US 6653305 | B2 | 20031125 | | |
| CA 2417050 | AA | 20020307 | CA 2001-2417050 | 20010818 |
| AU 2001084021 | A5 | 20020313 | AU 2001-84021 | 20010818 |
| EP 1315717 | A1 | 20030604 | EP 2001-962953 | 20010818 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004517048 | T2 | 20040610 | JP 2002-523888 | 20010818 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10042060 | A 20000826 |
| | | | US 2000-230389P | P 20000906 |
| | | | WO 2001-EP9537 | W 20010818 |

OTHER SOURCE(S): MARPAT 136:232315
 GI



AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-[(1,3-dioxolan-2-yl)methyl]methylanimo, (substituted) R4COCH2NHC2H2CH2OH, 2-oxomorphan-4-yl; R4 = H, alkyl; R3 = H, (alkoxy)alkoxy, cycloalkylalkoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy,

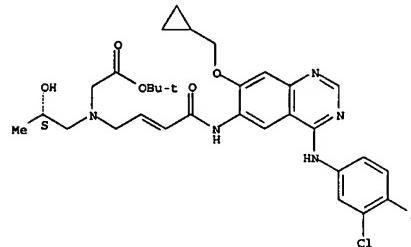
L3 ANSWER 45 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 tetracydropyran-4-yloxy, tetrahydrofuranylmethoxy, tetracydropyranylmethoxy; - = 1-3], were prepd. Thus, a mixt. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and disopropylethylamine in THF was dropwise treated under ice-cooling with BrCH2CH:CHCO2Cl (prepn. given) in CH2Cl2 followed by stirring for 1 h under ice-cooling and for 2 h at room temp. and addn. of (S)-[2-hydroxymethylamino]acetic acid tert-Bu ester in CH2Cl2 to give after stirring over night at room temp. and stirring for 5 h at 60° 64% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(N-(tert-butoxycarbonylmethyl)-N-((S)-2-hydroxyprop-1-yl)amino)-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. Several I inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC50 = 0.02-15 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN Glycine, N-[4-[(4-((3-chloro-4-fluorophenyl)amino)-7-(cyclopropylmethoxy)-6-quinazolinyl)amino]-4-oxo-2-butenyl]-1,1-dimethyl ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 46 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 ACCESSION NUMBER: 2002:171886 CAPLUS
 DOCUMENT NUMBER: 136:216758
 TITLE: Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit;
 Blech, Stefan; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma Kg, Germany
 SOURCE: PCT Int. Appl., 66 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

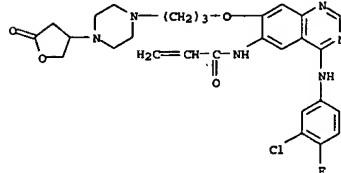
L3 ANSWER 46 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl)propoxy]quinazoline (prepn. given) in THF for 20 min and stirring at 0° up to completely conversion to give 31% 4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl)propoxy]-6-(vinylcarbonyl)aminoquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC50 = 12 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402496-84-8 CAPLUS

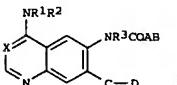
CN 2-Propenamide, N-[(4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2002018370 | A1 | 20020307 | WO 2001-EP9535 | 20010818 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, PR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10042061 | A1 | 20020307 | DE 2000-10042061 | 20000826 |
| CA 2417042 | AA | 20020307 | CA 2001-2417042 | 20010818 |
| AU 2001089814 | A5 | 20020313 | AU 2001-89814 | 20010818 |
| EP 1315716 | A1 | 20030604 | EP 2001-969610 | 20010818 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004507533 | T2 | 20040311 | JP 2002-523885 | 20010818 |
| US 2002082270 | A1 | 20020627 | US 2001-934753 | 20010822 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10042061 | A 20000826 |
| | | | US 2000-230119P | P 20000905 |
| | | | WO 2001-EP9535 | W 20010818 |

OTHER SOURCE(S): MARPAT 136:216758
 GI



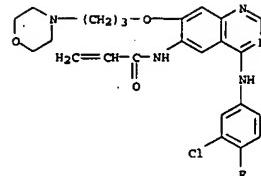
AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1-4-yl; B = H, (substituted) alkyl, alkylcarbonyl, CO2H, alkoxycarbonyl, aminocarbonyl, (di)alkylaminocarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, morpholinocarbonyl, alkylpiperazinylcarbonyl; C = (oxy)alkenyl, O; D = (substituted) pyrrolidinyl, piperidinyl, hexahydroazepinyl, piperazinyl, etc.], were prepared. Thus, a mixture of CH2:CHCO2H and Et3N was stirred for 45 min at -50° with CH2:CHCO2Cl in THF followed by dropwise addition

L3 ANSWER 47 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:122440 CAPLUS
 DOCUMENT NUMBER: 137:329330
 TITLE: Evaluation of the human serum albumin column as a discovery screening tool for plasma protein binding
 AUTHOR(S): Buchholz, Lisa; Cai, Chun-Hua; Andress, Larry; Cleton, Adriean; Brodfuehrer, Joanne; Cohen, Lucinda
 CORPORATE SOURCE: Dynamics and Metabolism, Department of Pharmacokinetics, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
 SOURCE: European Journal of Pharmaceutical Sciences (2002), 15(2), 209-215
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB A total of 69 compds. with a variety of chemical structures were assayed using a human serum albumin column in combination with UV and mass spectrometric detection. A moderate correlation, $R^2=0.661$, between the plasma protein binding, determined by traditional techniques of equilibrium dialysis or chromatog. retention factor ($k'/k'+1$) was observed. Disparity between the regression line and numerous samples was observed across the entire range of plasma protein binding. Attempts to discriminate between compds. from the data set to achieve better correlation based physico-chemical properties were unsuccessful. Good agreement was observed for retention times obtained with UV detection with mobile phase containing phosphate buffer and mass spectrometric detection with mobile phase containing acetate buffer. Essentially identical data were obtained for compds. analyzed in singlet or cassette for minimally or highly bound (>90% bound) compds. Anal. of cassettes containing compds. with plasma protein binding greater than 90% did not cause column overload, even at analyte concns. up to 100 μ g/mL. Diverse results were obtained when chromatog. retention was used to rank order various classes of compds. Better correlation with ordering from known binding was obtained when a compound class contained a wide range of protein binding, in contrast to when compds. within a given class were all highly bound.

IT 289499-45-2, PD 0183805
 RL: ANT (Analyte); ANST (Analytical study)
 (evaluation of human serum albumin column as a discovery screening tool for plasma protein binding)
 RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 47 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

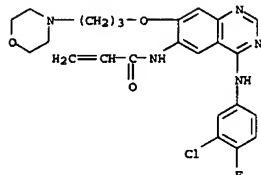
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 48 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:86818 CAPLUS
 DOCUMENT NUMBER: 136:395481
 TITLE: Differential sensitivity of cancer cells to inhibitors of the epidermal growth factor receptor family
 AUTHOR(S): Bishop, Philippa C.; Myers, Timothy; Robey, Robert; Fry, David W.; Liu, Edison T.; Blagosklonny, Mikhail V.; Bates, Susan E.
 CORPORATE SOURCE: Medicine Branch, NCI, NIH, Bethesda, MD, 20892, USA
 SOURCE: Oncogene (2002), 21(1), 119-127
 PUBLISHER: Nature Publishing Group
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Clin. responses to the HER1 (EGF receptor) inhibitors and HER2/neu/ErbB2 inhibitors correlate with high levels of receptor expression. However, a significant subset of patients with high receptor levels appear to be refractory to treatment. We have observed similar results in the 60 cell lines of the NCI Anti-Cancer Drug Screen using a panel of 11 selective HER1 inhibitors. As expected, low HER1-expressing cell lines were insensitive to HER1 inhibitors. In cell lines with high HER1 expression, low concns. of HER1 inhibitors potently inhibit both HER1 phosphorylation and the mitogen-activated protein kinase (MAPK) pathway. However, this inhibition did not always correlate with cellular arrest. High HER1-expressing cell lines can be subdivided into two groups based on their sensitivity to HER1 inhibitors. In the sensitive group, receptor and growth inhibition was concordant and occurred at submicromolar concns. of HER1 inhibitors. In the insensitive group, receptor inhibition occurred at a low concentration (< 1 M) but concns. that were ten times or higher were required for growth inhibition. Also, neither induction of p21 and cyclin D1 nor p53 status could explain the difference between sensitive and insensitive cells. Although EGF activated the MAPK pathway in all cell lines, only drug-sensitive cell lines responded to EGF (accelerated entry from G1 to S) and to HER1 inhibitors (G1 arrest) by changes in cell cycling. Furthermore, an EGF-dependent immortalized mammary epithelial cell line was extremely sensitive to a panel of HER1 inhibitors. We infer that independence from mitogen-mediated signaling confers insensitivity to HER1 inhibitors in a large subset of cancer cell lines.

IT 289499-45-2, NSC 709239
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USSE (Uses)
 (PD 183805; sensitivity of cancer cells to inhibitors of EGF receptor family)
 RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 48 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



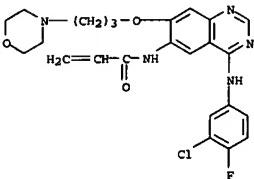
● 2 HCl

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 49 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:74864 CAPLUS
 DOCUMENT NUMBER: 137:134227
 TITLE: Epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy
 AUTHOR(S): Adjei, Alex A.
 CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA
 SOURCE: Drugs of the Future (2001), 26(11), 1087-1092
 CODEN: DRFDUD; ISSN: 0377-8282
 PUBLISHER: Prou Science
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review. Receptor tyrosine kinases are transmembrane proteins involved in signal transduction. They propagate growth factor signals from the cell surface to intracellular processes that control critical functions such as growth, differentiation, angiogenesis and inhibition of apoptosis. In malignancies, these signaling pathways are often exploited to optimize tumor growth and metastasis. One such family of receptor tyrosine kinases is the epidermal growth factor receptor (EGFR) tyrosine kinase. These receptors are overexpressed in a wide variety of epithelial cancers and have been implicated in tumor aggressiveness. Thus, targeting the EGFR tyrosine kinase has attracted considerable attention. This review will summarize current preclin. and clin. knowledge of the small-mol. oral inhibitors of the EGFR tyrosine kinase, which include ZD-1839, OSI-774, CI-1033, EKB-569, PKI-166, GW-2016 and BIBX-1382.

IT 289499-45-2, CI-1033
 RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (epidermal growth factor receptor tyrosine kinase inhibitors in cancer therapy)

RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quiazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS

L3 ANSWER 50 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2002:10449 CAPLUS
 DOCUMENT NUMBER: 136:74658
 TITLE: Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)-quiazolin-6-yl]acrylamide dihydrochloride
 INVENTOR(S): Barth, Hubert; Steiner, Klaus; Schneider, Simon; Huels, Dietmar; Muehlenfeld, Andreas; Westermayer, Manfred
 PATENT ASSIGNEE(S): Goedecke G.m.b.H., Germany
 SOURCE: PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|----------|
| WO 200200630 | A1 | 20020103 | WO 2001-EP6733 | 20010615 |
| W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NZ, PL, RO, RU, SG, SI, SK, SL, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, WG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10031971 | A1 | 20020110 | DE 2000-10031971 | 20000630 |
| EP 1299363 | A1 | 20030409 | EP 2001-962739 | 20010615 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 200101082 | A | 20030506 | BR 2001-12082 | 20010615 |
| JP 2004051902 | T2 | 20040122 | JP 2002-505378 | 20010615 |
| NZ 522001 | A | 20040730 | NZ 2001-522001 | 20010615 |
| EE 200200714 | A | 20040816 | EE 2002-714 | 20010615 |
| ZA 2002009717 | A | 20031201 | ZA 2002-9717 | 20021129 |
| BG 107352 | A | 20030731 | BG 2002-107352 | 20021204 |
| NO 2002006193 | A | 20030127 | NO 2002-6193 | 20021223 |
| US 2004034023 | A1 | 20040219 | US 2003-312173 | 20030404 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10031971 | 20000630 |
| AB | | | WO 2001-EP6733 | 20010615 |

AB Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quiazolin-6-yl]acrylamide-2HCl (I), processes for their preparation, as well as their use for the preparation of pharmaceuticals with irreversible tyrosine kinase inhibiting action are described.

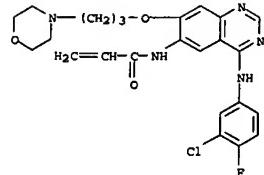
N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quiazolin-6-yl]acrylamide was dissolved in EtOH and treated with HCl to give I monohydrate (Form I). The compound was thermally stable when subjected to different thermal stress conditions.

IT 289499-45-29
 RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of polymorphic forms/hydrates of (chlorofluorophenylamino)morpholinylpropoxyquiazolinylacrylamide)

RN 289499-45-2 CAPLUS
 CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quiazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 50 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 50 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 51 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:935435 CAPLUS
 DOCUMENT NUMBER: 136:84677
 TITLE: Methods for enhancing antibody-induced cell lysis and treating cancer
 INVENTOR(S): Weiner, George; Hartmann, Gunther
 PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
 SOURCE: PCT Int. Appl., 312 pp.
 CODEN: PIKXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2001097843 | A2 | 20011227 | WO 2001-US20154 | 20010622 |
| WO 2001097843 | A3 | 20030123 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2410371 | AA | 20011227 | CA 2001-2410371 | 20010622 |
| US 2003026801 | A1 | 20030206 | US 2001-888326 | 20010622 |
| EP 1296714 | A2 | 20030402 | EP 2001-948684 | 20010622 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003535907 | T2 | 20031202 | JP 2002-503327 | 20010622 |
| PRIORITY APPLN. INFO.: | | | US 2000-213346P | P 20000622 |
| | | | WO 2001-US20154 | W 20010622 |

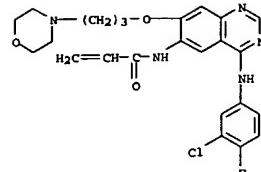
AB The invention relates to methods and products for treating cancer. In particular the invention relates to combinations of nucleic acids and antibodies for the treatment and prevention of cancer. The invention also relates to diagnostic methods for screening cancer cells.

IT 289499-45-2, PD 183805
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (immunostimulatory nucleic acids and antibody specific to CD20, CD22, CD19 or CD40 for inducing cell lysis and treating cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 51 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

L3 ANSWER 52 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 52 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:921399 CAPLUS
 DOCUMENT NUMBER: 137:72358
 TITLE: CI-1033, a pan-erbB tyrosine kinase inhibitor
 AUTHOR(S): Slichenmyer, William J.; Elliott, William L.; Fry, David W.
 CORPORATE SOURCE: Department of Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
 SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 80-85
 CODEN: SOLGAV; ISSN: 0093-7754

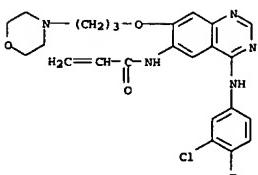
PUBLISHER: W. B. Saunders Co.
 DOCUMENT TYPE: Journal; General Review
 LANGUAGES: English

AB A review. Overexpression of the erbB family of receptor tyrosine kinases has been implicated in a variety of tumors including breast, lung, prostate, and brain. Most solid tumors express one or more of these receptors, which can often be related to tumor aggressiveness and poor patient prognosis. CI-1033, a pan-erbB tyrosine kinase inhibitor, is a clin. promising agent that is active against all four members of the erbB receptor tyrosine kinase family. In vitro studies of human cancer cell lines indicate that CI-1033 results in prompt, potent, and sustained inhibition of tyrosine kinase activity. This inhibition is highly selective for erbB1 (epidermal growth factor receptor), erbB2, erbB3, and erbB4 without inhibiting tyrosine kinase activity of receptors such as platelet-derived growth factor receptor, fibroblast growth factor receptor, and insulin receptor, even at high concns. Treatment of athymic nude mice bearing xenografts of human N433 epidermoid carcinoma, H125 non-small cell lung carcinoma, and SF-767 glioblastoma results in highly significant suppression of tumor growth. The major toxicity in animals is diarrhea, which is more severe at higher doses. In animal models, all side effects are reversible on cessation of treatment. Thus, CI-1033, which is currently undergoing phase I clin. trials, holds significant potential for use in a broad range of solid tumors.

IT 289499-45-2, CI-1033
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (CI-1033, a pan-erbB tyrosine kinase inhibitor)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

L3 ANSWER 53 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:921398 CAPLUS
 DOCUMENT NUMBER: 137:87979
 TITLE: Anticancer therapy targeting the ErbB family of receptor tyrosine kinases
 AUTHOR(S): Slichenmyer, William J.; Fry, David W.
 CORPORATE SOURCE: Departments of Oncology Clinical Development and Cancer Research, Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
 SOURCE: Seminars in Oncology (2001), 28(5, Suppl. 16), 67-79
 CODEN: SOLGAV; ISSN: 0093-7754
 PUBLISHER: W. B. Saunders Co.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Several agents that target one or more members of the erbB family of receptor tyrosine kinases are currently undergoing clin. investigation. The monoclonal antibody trastuzumab has been shown effective in erbB2-expressing metastatic breast cancer when administered as a single agent or in combination with cytotoxic chemotherapy. Toxicities associated with trastuzumab include infusion-related fever and chills, hypersensitivity reactions, and congestive heart failure. C225 is a monoclonal antibody directed against the epidermal growth factor receptor, which has shown encouraging antitumor activity in early clin. development. The orally active tyrosine kinase inhibitors show encouraging antitumor activity in preclin. models and early clin. trials. Members of this class currently in clin. development include ZD1839, OSI174, and CI-1033. Evidence to date suggests that the major role for erbB receptor-targeting drugs will be in combined therapy to enhance response to cytotoxic drugs, and in long-term monotherapy to maintain response and prevent disease progression or recurrence.

IT 289499-45-2, CI-1033

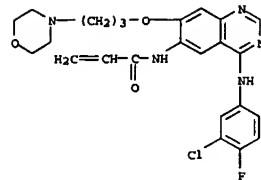
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

' (anticancer therapy targeting the ErbB family of receptor tyrosine kinases)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl], dihydrochloride (9CI) (CA INDEX NAMES)

L3 ANSWER 53 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 54 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:800795 CAPLUS
 DOCUMENT NUMBER: 136:95729
 TITLE: Evidence for epidermal growth factor receptor-enhanced chemosensitivity in combinations of cisplatin and the new irreversible tyrosine kinase inhibitor CI-1033
 AUTHOR(S): Gieseg, Michael A.; De Bock, Charles; Ferguson, Lynette R.; Denny, William A.
 CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical & Health Sciences, The University of Auckland, Auckland, 1000, N. Z.
 SOURCE: Anti-Cancer Drugs (2001), 12(8), 683-690
 CODEN: ANTDEV; ISSN: 0959-4973
 PUBLISHER: Lippincott Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Irreversible inhibitors of the epidermal growth factor receptor (EGFR) are showing promise in clin. trials. This report is the first to show that inhibition of the EGFR tyrosine kinase by an irreversible binder synergizes with cisplatin, at least in EGFR-overexpressing tissue culture cell lines in vitro. Unlike previous synergies demonstrated between ErbB2 blockade and DNA-damaging drugs, the synergy between the irreversible EGFR inhibitor and cisplatin does not appear to involve the repair of DNA-cisplatin adducts. Given the current clin. data, this combination may be of more than theor. interest.

IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (evidence for EGFR-enhanced chemosensitivity in combinations of cisplatin and CI-1033)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl], dihydrochloride (9CI) (CA INDEX NAMES)

L3 ANSWER 55 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:797778 CAPLUS
 DOCUMENT NUMBER: 136:112324
 TITLE: Sequential tumor biopsies in early phase clinical trials of anticancer agents for pharmacodynamic evaluation

AUTHOR(S): Dowlati, Afshin; Haaga, John; Remick, Scot C.; Spiro, Timothy P.; Gerson, Stanton L.; Liu, Lili; Berger, Sosanna J.; Berger, Nathan A.; Willson, James K. V.

CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine and Developmental Therapeutics Program, Ireland Cancer Center at University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, 44106, USA

SOURCE: Clinical Cancer Research (2001), 7(10), 2971-2976
 CODEN: CCREPA; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal
 LANGUAGE: English

AB In the setting of target-based anticancer drug development, it is critical to establish that the observed preclin. activity can be attributed to modulation of the intended target in early phase trials in human subjects. This paradigm of target modulation allows the authors to determine a Phase II or III dose (optimal biochem./biol. modulatory dose) that may not necessarily be the maximum tolerated dose. A major obstacle to target-based (often cytostatic) drug development has been obtaining relevant tumor tissue during clin. trials of these novel agents for laboratory anal. of the putative marker of drug effect. From 1989 to present, the authors have completed seven clin. trials in which the end point was a biochem. or biol. modulatory dose in human tumor tissues (not surrogate tissue). Eligibility enrollment required that patients have a biopsiable lesion either with computerized tomog. (CT) guidance or direct visualization and consent to sequential (pre and posttreatment) biopsies. A total of 192 biopsies were performed in 107 patients. All but 8 patients had sequential pre and posttreatment biopsies. Seventy-eight (73%) of the 107 patients had liver lesion biopsies. In eight patients, either one or both biopsies contained insufficient viable tumor tissue or no tumor tissue at all for anal. Of a total of 99 patients in whom the authors attempted to obtain paired biopsies, a total of 87 (88%) were successful. Reasons for failure included patient refusal for a second biopsy ($n = 2$), vasovaginal reaction with first biopsy precluding a second biopsy ($n = 1$), subcapsular hepatic bleeding ($n = 1$), and most commonly obtaining necrotic tumor, fibrous, or normal tissue in one of the two sequential biopsies ($n = 8$). This is the first and largest reported series demonstrating that with adequate precautions and experience, sequential tumor biopsies are feasible and safe during early phase clin. trials.

IT 289499-45-2, CI-1033

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (sequential human tumor biopsies in early phase clin. trials of anticancer agents for pharmacodynamic evaluation)

RN 289499-45-2 CAPLUS

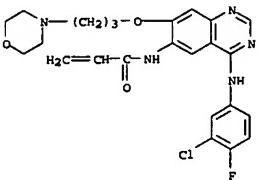
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl], dihydrochloride (9CI) (CA INDEX NAMES)

● 2 HCl

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 55 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



● 2 HCl

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 56 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:799777 CAPLUS
DOCUMENT NUMBER: 137:27578TITLE: A novel approach in the treatment of cancer: Targeting the epidermal growth factor receptor
AUTHOR(S): Ciardiello, Fortunato; Tortora, Giampaolo
CORPORATE SOURCE: Cattedra di Oncologia Medica. Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Università di Napoli "Federico II.", Naples, 80131, Italy
SOURCE: Clinical Cancer Research (2001), 7(10), 2958-2970
CODEN: CCREP4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signaling pathway. The results of a large body of preclin. studies and the early clin. trials thus far conducted suggest that targeting the EGFR could represent a significant contribution to cancer therapy. A variety of different approaches are currently being used to target the EGFR. The most promising strategies in clin. development include monoclonal antibodies to prevent ligand binding and small mol. inhibitors of the tyrosine kinase enzymic activity to inhibit autoprophosphorylation and downstream intracellular signaling. At least five blocking monoclonal antibodies have been developed against the EGFR. Among these, IMC-225 is a chimeric human-mouse monoclonal IgG1 antibody that has been the first anti-EGFR targeted therapy to enter clin. evaluation in cancer patients in Phase II and III studies, alone or in combination with conventional therapies, such as radiotherapy and chemotherapy. A number of small mol. inhibitors of the EGFR tyrosine kinase enzymic activity is also in development. OSI-774 and ZD1839 (Iressa) are currently in Phase II and III development, resp. ZD1839, a p.o. active, selective quinazoline derivative has demonstrated promising in vitro and in vivo antitumor activity. Preliminary results from Phase I and II trials in patients with advanced disease demonstrate that ZD1839 and OSI-774 have an acceptable tolerability profile and promising clin. efficacy in patients with a variety of tumor types. This mini-review describes the EGFR inhibitors in clin. development.

IT 289499-45-2, PD183805

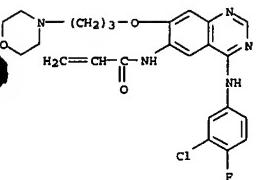
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting the epidermal growth factor receptor as a novel approach in the treatment of cancer)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 56 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



● 2 HCl

REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 57 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:762992 CAPLUS
DOCUMENT NUMBER: 135:303907TITLE: Preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction.
INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit;
Blech, Stefan; Solca, Flavio
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIKXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

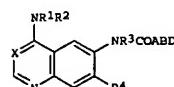
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| WO 2001077104 | A1 | 20011018 | WO 2001-EP3694 | 20010331 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BV, KG, KZ, MD, RU, TJ, TM, RW, GH, GM, KE, MM, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10017539 | A1 | 20011011 | DE 2000-10017539 | 20000408 |
| DE 10040525 | A1 | 20020228 | DE 2000-10040525 | 20000818 |
| CA 2403152 | AA | 20011018 | CA 2001-2403152 | 20010331 |
| AU 2001063831 | AS | 20011023 | AU 2001-63831 | 20010331 |
| EP 1280798 | A1 | 20030205 | EP 2001-93076 | 20010331 |
| R: AT, BE, CH, DE, DK, ES, FR, GR, IE, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003530395 | T2 | 20031014 | JP 2001-575577 | 20010331 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10017539 | A 20000408 |
| | | | DE 2000-10040525 | A 20000818 |
| | | | WO 2001-EP3694 | W 20010331 |

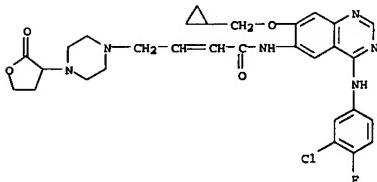
OTHER SOURCE(S): MARPAT 135:303907

GI



AB Title compds. [I]; X = NCN, N; R1 = H, alkyl; R2 = (substituted) Ph, PhCH2, PhCH=CH2; R3 = H, alkyl; R4 = H, alkoxy, cycloalkoxy, cycloalkylalkoxy; A = (substituted) vinylene; B = bond; (fluoro)alkylene; D = substituted pyrrolidinyl, piperidinyl, piperazinyl, etc.), were prepared. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(piperazin-1-yl)-1-oxo-1-butene-1-yl)amino]-7-cyclopropylmethoxyquinazoline (preparation given) in THF was treated with Et3N and then with 3-bromodihydrofuran-2-one in THF under ice cooling followed by stirring for 48 h at room temperature to give 56% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-(4-(2-oxotetrahydrofuran-3-yi)piperazin-1-yl)-1-oxo-1-butene-1-yl)amino]-7-

L3 ANSWER 57 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)
 cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERC cells with IC₅₀ = 0.05 nM.
 IT 365532-35-0P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)
 RN 365532-35-0 CAPIUS
 CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

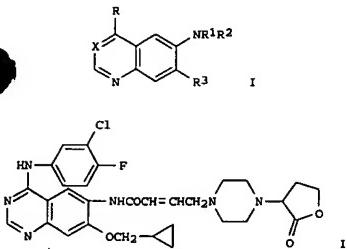
L3 ANSWER 58 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)
 2001-747043 CAPIUS
 135:303901
 TITLE: Bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma KG, Germany
 Ger. Offen., 28 pp.
 SOURCES:
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|---|----------|------------------|------------|
| DE 10017539 | A1 | 20011011 | DE 2000-10017539 | 20000408 |
| US 2001044435 | A1 | 20011122 | US 2001-816003 | 20010323 |
| US 6627634 | B2 | 20030930 | | |
| CA 2403152 | AA | 20011018 | CA 2001-8403152 | 20010331 |
| WO 2001077104 | A1 | 20011018 | WO 2001-EP3694 | 20010331 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, T2, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CP, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| AU 2001063831 | A5 | 20011023 | AU 2001-63831 | 20010331 |
| EP 1280798 | A1 | 20030205 | EP 2001-938076 | 20010331 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| JP 2003530395 | T2 | 20031014 | JP 2001-575577 | 20010331 |
| PRIORITY APPLN. INFO.: | | | DE 2000-10017539 | A 20000408 |
| | | | DE 2000-10040525 | A 20000818 |
| | | | WO 2001-EP3694 | W 20010331 |

OTHER SOURCE(S): MARPAT 135:303901

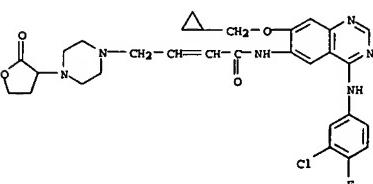
GI

L3 ANSWER 58 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)



AB Bicyclic heterocycles I (X = N, CCN; R = substituted NH₂; R₁ = H, alkyl; R₂ = acyl; R₃ = H, (un)substituted alkoxy, cycloalkoxy, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl) were prepared for use as inhibitors of tyrosine kinase-mediated signal transduction for treatment of tumors and diseases of the lung and airway. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-7-fluoro-6-nitroquinazoline was treated with cyclopropylmethanol, followed by reduction to the amine, reaction with 4-bromocrotonic acid and N-tert.-butyloxycarbonylpiperazine, and deblocking to give the quinazoline II. II had an IC₅₀ for inhibition of epidermal growth factor dependent proliferation of 0.05 nM.

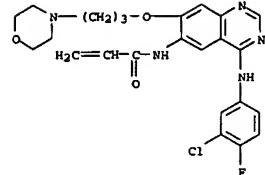
IT 365532-35-0P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)
 RN 365532-35-0 CAPIUS
 CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl)- (9CI) (CA INDEX NAME)



L3 ANSWER 58 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)

L3 ANSWER 59 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:713163 CAPLUS
 DOCUMENT NUMBER: 135:267215
 TITLE: Combined treatment with keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor for reducing EGFR inhibitor-associated epithelial toxicity
 INVENTOR(S): Miller, Penelope Elizabeth; Moyer, James Dale
 PATENT ASSIGNEE(S): Pfizer Products, Inc., USA; OSI Pharmaceuticals, Inc.
 SOURCES: PCT Int. Appl., 24 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

L3 ANSWER 59 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| WO 2001070255 | A2 | 20010927 | WO 2001-US8207 | 20010315 |
| WO 2001070255 | A3 | 20020228 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MN, MM, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TW, CA 2403721 AA 20010927 CA 2001-2403721 20010315 | | | | |
| US 2002061304 | A1 | 20020523 | US 2001-808751 | 20010315 |
| EP 1276496 | A2 | 20030122 | EP 2001-916662 | 20010315 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, JP 2003527437 T2 20030916 JP 2001-568452 20010315 | | | | |
| US 2004071697 A1 20040415 US 2003-458072 20030610 | | | | |
| US 2000-190697P US 2000-190697P P 20000320 | | | | |
| US 2001-808751 B1 20010315 | | | | |
| WO 2001-US8207 W 20010315 | | | | |

PRIORITY APPLN. INFO.: AB Comps. and methods are provided for treating the epithelial toxicity caused by administering to a human cancer patient an epidermal growth factor receptor (EGFR) inhibitor. The pharmaceutical composition preferably comprises an EGFR inhibitor and a keratinocyte growth factor (KGF) in a pharmaceutically acceptable carrier. The method of treatment comprises co-administering to the patient a therapeutically effective amount of KGF with the EGFR inhibitor.

IT 289499-45-2, PD 183805

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (keratinocyte growth factor and epidermal growth factor receptor (EGFR) inhibitor combination treatment for reducing EGFR inhibitor-associated epithelial toxicity)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 60 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:516932 CAPLUS
 DOCUMENT NUMBER: 135:313144
 TITLE: The 4-anilinoquinazoline class of inhibitors of the erbB family of receptor tyrosine kinases
 AUTHOR(S): Denny, William A.
 CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
 SOURCE: Farmaco (2001), 56(1-2), 51-56
 PUBLISHER: Elsevier Science S.A.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The erbB family of receptor tyrosine kinase enzymes, and particularly EGFR and HER2/neu, have become important targets for potential anticancer drugs. The substrate/protein binding site theor. is the more attractive intracellular target on these enzymes possessing lower homol. than the ATP site between different receptor kinases. However, a major breakthrough in this field was the discovery that 4-anilinoquinazolines are potent and selective inhibitors, despite binding at the ATP site. The very tight structure-activity relationship shown by these compds. suggested a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. A unique cysteine (Cys-73) adjacent to the quinazoline binding site has prompted the development of irreversible inhibitors that target this residue. Three 4-anilinoquinazoline analogs (two reversible and one irreversible inhibitor) have been evaluated clin. as anticancer drugs. Data from the most advanced, the reversible inhibitor trastuzumab, suggest that this class of compds. may be of value in cancer chemotherapy.

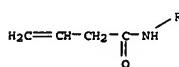
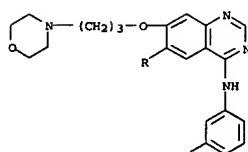
IT 367518-74-9

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (4-anilinoquinazoline class of inhibitors of erbB family of receptor tyrosine kinases)

RN 367518-74-9 CAPLUS

CN 3-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 60 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 61 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:380438 CAPLUS
 DOCUMENT NUMBER: 135:24657
 TITLE: Selective cellular targeting: multifunctional delivery vehicles
 INVENTOR(S): Glazier, Arnold
 PATENT ASSIGNEE(S): Drug Innovation & Design, Inc., USA
 SOURCE: PCT Int. Appl., 981 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 2001036003 | A2 | 20010525 | WO 2000-US31262 | 20001114 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BP, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2391534 | AA | 20010525 | CA 2000-2391534 | 20001114 |
| AU 2001016075 | A5 | 20010530 | AU 2001-16075 | 20001114 |
| EP 1255567 | A1 | 20021113 | EP 2000-978631 | 20001114 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2003138432 | A1 | 20030724 | US 2000-738625 | 20001215 |
| PRIORITY APPLN. INFO.: | | | US 1999-165485P | P 19991115 |
| | | | US 2000-239478P | P 20001011 |
| | | | US 2000-241937P | P 20001020 |
| | | | US 2000-241939P | P 20001020 |
| | | | W 2000-US31262 | W 20001114 |
| | | | US 2000-712465 | B1 20001115 |

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional products or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

IT 341551-76-6

RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(multifunctional delivery vehicles for selective cellular targeting of drugs)

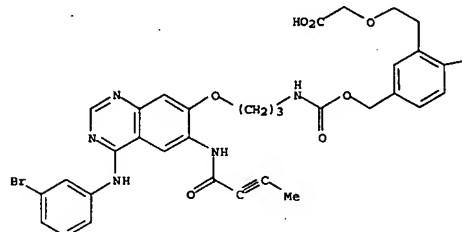
RN 341551-76-6 CAPLUS

CN 2,4-Dioxa-7,10-diaza-3-phosphoundecan-11-oic acid, 9-[[[4-[[[[[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-butynyl)amino]-7-

L3 ANSWER 61 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 quinazolin-9(yloxy)propyl]amino]carbonyl]oxy)methyl]-2-(2-[carboxymethoxy]ethyl)phenyl)dithio[methyl]-1-(9H-fluoren-9-yl)-3-(9H-fluoren-9-ylmethyl) ester, 3-oxide, (9R)- (9CI) (CA INDEX NAME)

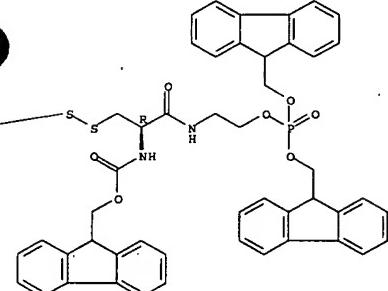
Absolute stereochemistry.

PAGE 1-A



L3 ANSWER 61 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PAGE 1-B



L3 ANSWER 62 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:367797 CAPLUS
 DOCUMENT NUMBER: 135:102151
 TITLE: Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition

AUTHOR(S): Nelson, James M.; Fry, David W.
 CORPORATE SOURCE: Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
 SOURCE: Journal of Biological Chemistry (2001), 276(18), 14842-14847
 PUBLISHER: CODEN: JBCHA3; ISSN: 0021-9258
 American Society for Biochemistry and Molecular Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The ErbB receptor family is implicated in the malignant transformation of several tumor types and is over-expressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and gemcitabine, either singly or in combination, kill tumor cells was examined in two breast lines, MDA-MB-453 and BT474; both overexpress the Erbb-2 receptor. CI-1033, a potent inhibitor of the ErbB family of receptor tyrosine kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. Gemcitabine treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after gemcitabine produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-kinase inhibitor LY294002 and the MAPK/ERK kinase inhibitor PD098059 in combination with gemcitabine produced the same results as the combination of CI-1033 and gemcitabine. P38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under untreated conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. Gemcitabine did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and gemcitabine in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.

IT 267243-28-7, CI-1033

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

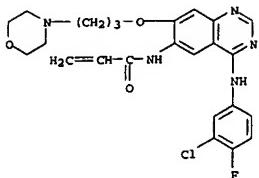
(Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in human breast carcinoma in response to ErbB receptor family inhibition)

RN 267243-28-7 CAPLUS

CN 2-Propenamide, N-[(3-chloro-4-fluorophenyl)amino]-7-[(4-morpholinyl)propoxy]-6-quinazolinyl- (9CI) (CA INDEX NAME)

L3 ANSWER 62 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 63 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:338332 CAPLUS
 DOCUMENT NUMBER: 134:336209
 TITLE: EGFR tyrosine kinase inhibitors for the prevention of breast cancer
 INVENTOR(S): Bundred, Nigel James
 PATENT ASSIGNEE(S): The University of Manchester, UK
 SOURCE: PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|------------|
| WO 2001032155 | A2 | 20010510 | WO 2000-GB4190 | 20001101 |
| WO 2001032155 | A3 | 20020510 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KS, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2389411 | AA | 20010510 | CA 2000-2389411 | 20001101 |
| BR 2000015194 | A | 20020618 | BR 2000-15194 | 20001101 |
| EP 1272188 | A2 | 20030108 | EP 2000-973002 | 20001101 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, PI, RO, MK, CY, AL | | | | |
| JP 2003513035 | T2 | 20030408 | JP 2001-534360 | 20001101 |
| NO 2002002065 | A | 20020624 | NO 2002-2065 | 20020430 |
| ZA 2002003431 | A | 20021209 | ZA 2002-3431 | 20020430 |
| PRIORITY APPLN. INFO.: | | | GB 1999-25958 | A 19991102 |
| | | | WO 2000-GB4190 | W 20001101 |

AB An EGFR tyrosine kinase inhibitor (e.g. ZD1839) is used in the manufacture of a medicament for use in (a) reducing the transformation of epithelial cells from a normal state to a malignant state in an invasive breast cancer free human; and/or (b) reducing the transformation of epithelial cells from an intermediate state, between normal epithelium and malignant invasive epithelium, to a malignant state in an invasive breast cancer free human; and/or (c) causing substantial reversion of epithelial tissue back to a normal state from an intermediate state between normal epithelium and malignant invasive epithelium.

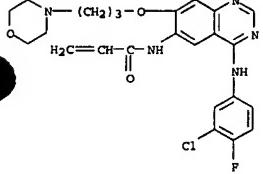
IT 289499-45-2
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(4-morpholinyl)propoxy]-6-quinazolinyl-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 63 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

(Continued)



●2 HC1

L3 ANSWER 64 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:125550 CAPLUS

DOCUMENT NUMBER: 134:348032

TITLE: The HER tyrosine kinase inhibitor CI1033 enhances cytotoxicity of 7-ethyl-10-hydroxycamptothecin and topotecan by inhibiting breast cancer resistance protein-mediated drug efflux

AUTHOR(S): Erlichman, Charles; Boerner, Scott A.; Hallgren, Christopher G.; Spieker, Rebecca; Wang, Xiao-Yang; James, C. David; Scheffer, George L.; Maliepaard, Marc; Ross, Douglas D.; Bible, Keith C.; Kaufmann, Scott H.

CORPORATE SOURCE: Division of Medical Oncology, Mayo Clinic, Mayo Graduate School, Rochester, MN, 55905, USA

SOURCES: Cancer Research (2001), 61(2), 739-748

CODEN: CIREAS; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Because the activities of HER family members are elevated and/or aberrant in a variety of human neoplasms, these cell surface receptors are receiving increasing attention as potential therapeutic targets. In the present study, we examined the effect of combining the HER family tyrosine kinase inhibitor CI1033 (PDT 183905) with the topoisomerase (topo) I poison 7-ethyl-10-hydroxycamptothecin (SN-38), the active metabolite of irinotecan, in a number of different cell lines. Colony-forming assays revealed that the antiproliferative effects of simultaneous treatment with CI1033 and SN-38 were synergistic in T98G glioblastoma cells and HCT8 colorectal carcinoma cells, whereas sequential treatments were additive at best. In addition, studies examining the mechanistic basis for these findings in T98G cells, immunoblotting revealed that the inhibitory effects of CI1033 on epidermal growth factor receptor autophosphorylation were unaffected by SN-38. Likewise, CI1033 had no effect on topo I polypeptide levels, localization, or activity. Nonetheless, CI1033 markedly enhanced the number of covalent topo I-DNA complexes stabilized by SN-38 or the related agent topotecan (TPT). Anal. of intracellular SN-38 levels by high-performance liquid chromatog. and intracellular TPT levels by flow microfluorometry revealed that CI1033 increased the steady-state accumulation of SN-38 and TPT by 9.4 ± 1.9- and 1.8 ± 0.2-fold, resp. Further evaluation revealed that the initial rate of TPT uptake was unaffected by CI1033, whereas the rate of efflux was markedly diminished. Addnl. studies demonstrated that T98G and HCT8 cells express the breast cancer resistance protein (BCRP), a recently cloned ATP binding cassette transporter. Moreover, CI1033 enhanced the uptake and cytotoxicity of SN-38 and TPT in cells transfected with BCRP but not empty vector. Conversely, CI1033 accumulation was diminished in cells expressing BCRP, suggesting that CI1033 is a substrate for this efflux pump. These results indicate that CI1033 can modulate the accumulation and subsequent cytotoxicity of two widely used topo I poisons in cells that have no history of previous exposure to these agents.

IT 289499-45-2, CI 1033

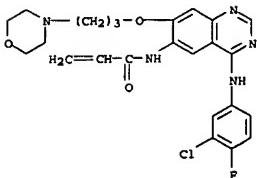
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(HER tyrosine kinase inhibitor CI1033 interactions with SN-38 and topotecan in cancer treatment)

RN 289499-45-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(4-morpholinyl)propoxy]-6-quinazolinyl-, dihydrochloride (9CI) (CA INDEX NAME)

L3 ANSWER 64 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



●2 HCl

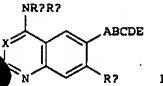
REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 65 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:911231 CAPLUS
 DOCUMENT NUMBER: 134:71599
 TITLE: Preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors.
 INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Metz, Thomas;
 Solca, Flavio; Jung, Birgit; Baum, Anke
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
 SOURCE: PCT Int. Appl., 104 pp.
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-------------------|------------|
| WO 2000078735 | A1 | 20001228 | WO 2000-EP5547 | 20000616 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, DE: 19928281 | A1 | 20001228 | DE 1999-19928281 | 19990621 |
| DE 10023085 | A1 | 20011115 | DE 2000-10023085 | 20000511 |
| CA 2375259 | AA | 20001228 | CA 2000-2375259 | 20000616 |
| BR 2000011834 | A | 20020312 | BR 2000-11834 | 20000616 |
| EP 1194418 | A1 | 20020410 | EP 2000-936888 | 20000616 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, TR: 200103692 | T2 | 20021021 | TR 2001-200103692 | 20000616 |
| JP 2003502410 | T2 | 20030121 | JP 2001-504901 | 20000616 |
| EE 200100695 | A | 20030217 | EE 2001-695 | 20000616 |
| AU 775285 | B2 | 20040729 | AU 2000-52214 | 20000616 |
| NZ 516633 | A | 20040924 | NZ 2000-516633 | 20000616 |
| BG 106189 | A | 20020830 | BG 2001-106189 | 20011207 |
| US 2002169180 | A1 | 20021114 | US 2001-16280 | 20011210 |
| NO 2001006185 | A | 20011218 | NO 2001-6185 | 20011218 |
| ZA 2001010351 | A | 20020618 | ZA 2001-10351 | 20011218 |
| PRIORITY APPLN. INFO.: | | | DE 1999-19928281 | A 19990621 |
| | | | US 1999-146644P | P 19990730 |
| | | | DE 2000-10023085 | A 20000511 |
| | | | WO 2000-EP5547 | W 20000616 |

OTHER SOURCE(S): MARPAT 134:71599
GI

L3 ANSWER 65 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



AB Title compds. [I]; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, PhCH2CH2; Rc = (substituted) cycloalkoxy, cycloalkylalkoxy; A = (alkyl-substituted) imino; B = CO, SO2; C = (substituted) allenylene, vinylene, butadienylene, ethynylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, carbonyloxylalkylene, carbonyliminoalkylene, bond, etc.; E = amino, (substituted) alkylamino, dialkylamino, etc.; I, were prepared. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propoxy]quinazoline (preparation given) in CH2Cl2 containing Et3N at -10° was treated with acryloyl chloride in THF to give 35% 4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propoxyl]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation of F/L HERC cells with IC50 = <0.35 nM.

IT 314771-08-9P RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPM (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses); (preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors)

RN 314771-08-9 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quiazolinyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 66 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:828300 CAPLUS
 DOCUMENT NUMBER: 135:57892
 TITLE: Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor
 AUTHOR(S): Rao, G. S.; Murray, S.; Ethier, S. P.
 CORPORATE SOURCE: Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2000), 48(5), 1519-1528

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: Overexpression of the ErbB family of growth factor receptors is present in a wide variety of human tumors and is correlated with poor prognosis. The purpose of this study was to determine the effects of a novel small mol. ErbB tyrosine kinase inhibitor, CI-1033, in combination with ionizing radiation on breast cancer cell growth and survival. Materials & Methods: Growth assays were performed on ErbB-overexpressing human breast cancer cells developed in our laboratory in the presence of 0.1-1.0 μM CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing radiation with or without CI-1033. For some expts., clonogen nos., defined as the product of surviving fraction and total number of cells, were calculated at each time point during a course of multifraction radiation. Results: CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. A single 18-h exposure of 1 μM CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly administration resulted in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and radiation (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to radiation alone. In a multifraction experiment, exposure to CI-1033 and three 5-Gy fractions of gamma radiation decreased the total number of clonogens in the population by 65-fold compared to radiation alone. Conclusion: CI-1033 results in potent growth inhibition and modest cytotoxicity of ErbB-overexpressing breast cancer cells, and has synergistic effects when combined with ionizing radiation. These data suggest that CI-1033 may have excellent clin. potential both alone and in combination with radiation therapy.

IT 267243-38-7, CI-1033

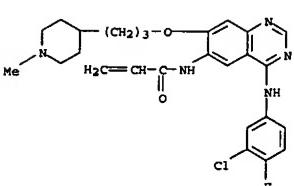
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(radiosensitization of human breast cancer cells by ErbB family receptor tyrosine kinase inhibitor)

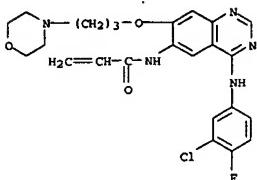
RN 267243-38-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quiazolinyl]- (9CI) (CA INDEX NAME)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



L3 ANSWER 66 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:628125 CAPLUS
 DOCUMENT NUMBER: 133:207919
 TITLE: Preparation of 4-amino-quinazoline and quinoline derivatives having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases

INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas; Solca, Flavio; Blech, Stefan
 PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K.-G., Germany
 SOURCE: PCT Int. Appl., 232 pp.

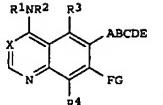
DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|----------|
| WO 2000051991 | A1 | 20000908 | WO 2000-EP1496 | 20000224 |
| W: AE, AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TU, TZ, RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UC, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BP, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| DE 19900567 | A1 | 20000831 | DE 1999-19908567 | 19990227 |
| DE 19911366 | A1 | 20000921 | DE 1999-19911366 | 19990315 |
| DE 19928306 | A1 | 20001228 | DE 1999-19928306 | 19990621 |
| DE 19954816 | A1 | 20010517 | DE 1999-19954816 | 19991113 |
| CA 2361174 | AA | 20000908 | CA 2000-2361174 | 20000224 |
| EP 1157011 | A1 | 20011128 | EP 2000-910695 | 20000224 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 2000008524 | A | 20011218 | BR 2000-8524 | 20000224 |
| JP 2002538145 | T2 | 20021112 | JP 2000-602218 | 20000224 |
| EE 200100449 | A | 20021216 | EE 2001-449 | 20000224 |
| BG 105765 | A | 20020329 | BG 2001-105765 | 20010801 |
| HR 200100617 | A1 | 20021031 | HR 2001-617 | 20010823 |
| NO 2001004114 | A | 20011015 | NO 2001-4114 | 20010824 |
| PRIORITY APPLN. INFO.: | | | | |
| DE 1999-19908567 | A | 19990227 | | |
| DE 1999-19911366 | A | 19990315 | | |
| DE 1999-19928306 | A | 19990621 | | |
| US 1999-149329P | P | 19990817 | | |
| DE 1999-19954816 | A | 19991113 | | |
| WO 2000-EP1496 | W | 20000224 | | |

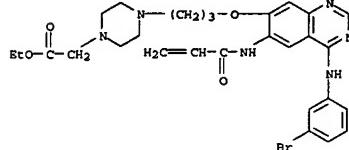
OTHER SOURCE(S): MARPAT 133:207919
 GI

L3 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

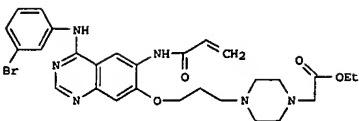


I

L3 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



II

AB Title compds. [I]; R1 = H, Cl-C4-alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3, R4 independently = H, F, Cl, CH3O, CH3OC(CH3)2, (CH3)2NCH2, (CH3)2NCH2, pyrrolidino, piperidino, morpholino; X = C(CN), N; A = O, NH, (C1-C4)-alkylN; B = CO, SO2; C = 1,3-allenyleno, 1,1-vinyliene, 1,2-vinyliene, 1,3-butadien-1,4-ylene, with CH3, CF3 substitution; D = alkylene, CO-alkylene, SO2-alkylene, CO, SO2; E = HOCO(CH2)nNR5; (HO)2P(O)(CH2)nNR5; n = 1-6; RS = H, alkyl tautomeric, stereoisomers, and physiol. acceptable salts are prepared and having valuable pharmacol. properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases. Title compds. are useful for treating tumoral diseases, diseases of the lungs and respiratory tract. Thus, the title compound II was prepared and tested by Cell Titer 96™ Aqueous Nonradioactive Cell Proliferation Assay.

IT 289700-58-9

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)

RN 289700-58-9 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[(4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl)oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 68 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:607393 CAPLUS

DOCUMENT NUMBER: 133:207916

TITLE: Preparation of aminoquinazolines as epidermal growth factor receptor inhibitors.

INVENTOR(S): Himmelbach, Frank; Langkopf, Elke; Jung, Birgit;

Metz, Thomas

PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma K-G, Germany

SOURCE: Ger. Offen., 26 pp.

DOCUMENT TYPE: Patent

LANGUAGE: German

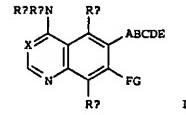
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|----------|
| DE 19908567 | A1 | 20000831 | DE 1999-19908567 | 19990227 |
| CA 2361174 | AA | 20000908 | CA 2000-2361174 | 20000224 |
| WO 2000051991 | A1 | 20000908 | WO 2000-EP1496 | 20000224 |
| W: AB, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, DE, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, LZ, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| NZ 513802 | A | 20010928 | NZ 2000-513802 | 20000224 |
| EP 1157011 | A1 | 20011128 | EP 2000-910695 | 20000224 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 2000008524 | A | 20011218 | BR 2000-8524 | 20000224 |
| JP 2002538145 | T2 | 20021112 | JP 2000-602218 | 20000224 |
| EE 200100449 | A | 20021216 | EE 2001-449 | 20000224 |
| ZA 2001005983 | A | 20020920 | ZA 2001-5983 | 20010720 |
| BG 105765 | A | 20020329 | BG 2001-105765 | 20010801 |
| HR 2001000617 | A1 | 20021031 | HR 2001-617 | 20010823 |
| NU 2001004114 | A | 20011015 | NU 2001-4114 | 20010824 |
| PRIORITY APPLN. INFO.: | | | | |
| DE 1999-19908567 | A | 19990227 | | |
| DE 1999-19911366 | A | 19990315 | | |
| DE 1999-19928306 | A | 19990621 | | |
| US 1999-149329P | P | 19990817 | | |
| DE 1999-19954816 | A | 19991113 | | |
| WO 2000-EP1496 | W | 20000224 | | |

OTHER SOURCE(S): MARPAT 133:207916
GI

L3 ANSWER 68 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



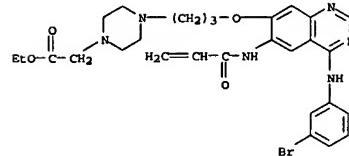
AB Title compds. (I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, 1-phenylethyl; Rc, Rm = H, F, Cl, MeO, (methoxy-, dimethylamino-, diethylamino-, pyrrolidino-, piperidino-, morpholino- substituted) Me; X = N, NCC; A = O, alkylimino; B = CO, SO2; C = (Me- or F3C-substituted) allenylene, vinylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, etc.; E, G = (substituted) R62CYNR5, etc.; R5 = H, (substituted) alkyl; R6 = H, (substituted) alkyl, cycloalkyl, alkenyl, alkyanyl, etc.; F = alkylene, oxalkylene, O; FG = H, F, Cl, alkoxy, etc.), were prepared. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-[4-(ethoxycarbonyl)methyl]piperazin-1-yl]propoxyquinazoline (preparation given) in CH2Cl2 containing Et3N was treated with acryloyl chloride in CH2Cl2 at -10° to give 62% 4-[(3-bromophenyl)amino]-7-[3-[4-[(ethoxycarbonyl)methyl]piperazin-1-yl]propoxy]-6-[(vinylcarbonyl)aminol]quinazoline. The latter inhibited EGF-dependent proliferation with IC50 = 2.6 nM.

IT 289700-58-9

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses); (preparation of aminoquinazolines as epidermal growth factor receptor inhibitors)

RN 289700-58-9 CAPLUS

CN 1-Piperazineacetic acid, 4-[(4-[(3-bromophenyl)amino]-6-((1-oxo-2-propenyl)amino)-7-quinazolinyl)oxy]propyl-, ethyl ester (9CI) (CA INDEX NAME)



L3 ANSWER 69 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:481416 CAPLUS

DOCUMENT NUMBER: 134:215784

TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylaminol)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. [Erratum to document cited in CA132:317628]

AUTHOR(S): Smaill, Jeff B.; Newcastle, Gordon W.; Bridges, Alexander J.; Zhou, Hairong; Showalter, H. D. Hollis; Fry, David W.; Nelson, James M.; Sherwood, Veronika; Elliott, William L.; Vincent, Patrick W.; DeJohn, Dana E.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Denny, William A.

CORPORATE SOURCE: Auckland Cancer Society Research Centre, Faculty

Medical and Health Sciences, The Univ. Auckland,

Auckland, N. Z.

SOURCE: Journal of Medicinal Chemistry (2000), 43(16), 3199

CODEN: JMMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Six author names were inadvertently omitted from the author contribution line. The complete author list is as follows: Jeff B. Smaill, Gordon W. Newcastle, Alexander J. Bridges, Hairong Zhou, H. D. Hollis Showalter, David W. Fry, James M. Nelson, Veronika Sherwood, William L. Elliott, Patrick W. Vincent, Dana E. DeJohn, Joseph A. Loo, Kenneth D. Greis, O. Helen Chan, Eric L. Reyner, Elke Lipka, and William A. Denny.

IT 198959-99-8 CAPLUS

RN 198959-99-8 CAPLUS

CN 2-Propenamide, N-4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl- (9CI) (CA INDEX NAME)

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2000031048 | A1 | 20000602 | WO 1999-US22116 | 19990923 |
| W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LZ, LR, LT, LV, MG, NO, NZ, PL, RO, SC, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IR, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 23497291 | AA | 20000602 | CA 1999-2349721 | 19990923 |
| AU 9962612 | A1 | 20000613 | AU 1999-62612 | 19990923 |
| AU 763626 | B2 | 20030731 | | |
| BR 9915487 | A | 20010731 | BR 1999-15487 | 19990923 |
| EP 1131304 | A1 | 20010912 | EP 1999-949821 | 19990923 |
| EP 1131304 | B1 | 20021204 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002530386 | T2 | 20020917 | JP 2000-582876 | 19990923 |
| ES 200100271 | A | 20020105 | ES 2001-271 | 19990923 |
| AT 229008 | E | 20021215 | AT 1999-949821 | 19990923 |
| ES 2188254 | T3 | 20030616 | ES 1999-949821 | 19990923 |
| NZ 512189 | A | 20031031 | NZ 1999-512189 | 19990923 |
| SK 283688 | B6 | 20031202 | SK 2001-657 | 19990923 |
| ZA 2001003535 | A | 20020802 | ZA 2001-3535 | 20010502 |
| US 6344458 | B1 | 20020205 | US 2001-311991 | 20010516 |
| NO 2001002465 | A | 20010713 | NO 2001-2465 | 20010518 |
| BG 105608 | A | 20020131 | BG 2001-105608 | 20010615 |

PRIORITY APPLN. INFO.: US 1998-109065P P 19981119 W 19990923

AB The title compound that is an irreversible inhibitor of tyrosine kinases such as EGFR, erbB2, and erbB4, and inhibitor of the tyrosine phosphorylation of erbB3 and VEGF secretion (biol. data were given), was prepared. The title compound is useful in treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis.

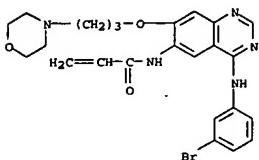
IT 198959-99-8 CAPLUS

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses); (preparation of N-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl)acrylamide as an irreversible inhibitor of tyrosine kinases)

RN 198959-99-8 CAPLUS

CN 2-Propenamide, N-4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl- (9CI) (CA INDEX NAME)

L3 ANSWER 70 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

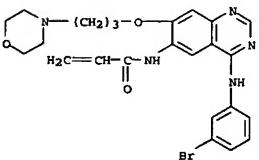


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 71 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2000:164843 CAPLUS
 DOCUMENT NUMBER: 132:317628
 TITLE: Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions
 AUTHOR(S): Smaili, Jeff B.; Newcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.
 CORPORATE SOURCE: Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
 SOURCES: Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
 CODEN: JMCMAR; ISSN: 0022-2623
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxymine side chains were prepared by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepared from 7-bromo-6-fluoropyrido[3,2-d]pyrimidines via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxymine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC50(app) values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the observed lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aqueous solubility, potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.

IT 198959-99-8P
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP

L3 ANSWER 71 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (antitumor and EGFR enzyme-inhibiting SAR of quinazolines)
 RN 198959-99-8 CAPLUS
 CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 72 OF 73 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1999:113656 CAPLUS
 DOCUMENT NUMBER: 130:168387
 TITLE: Irreversible inhibitors of tyrosine kinases
 INVENTOR(S): Bridges, Alexander James
 PATENT ASSIGNEE(S): Warner-Lambert Company, USA
 SOURCE: PCT Int. Appl., 124 pp.
 CODEN: PIXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

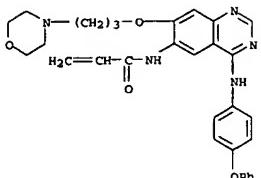
| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 9906378 | A1 | 19990211 | WO 1998-US15784 | 19980729 |
| W, AL, AU, BA, BB, BG, BR, CA, CN, CZ, DE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW, GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9887607 | A1 | 19990222 | AU 1998-87607 | 19980729 |
| US 6127274 | A | 20001003 | US 1999-269545 | 19990325 |
| US 6562818 | B1 | 20030513 | US 2000-593031 | 20000613 |
| PRIORITY APPLN. INFO.: | | | US 1997-54060P | P 19970729 |
| | | | WO 1998-US15784 | W 19980729 |
| | | | US 1999-269545 | A3 19990325 |

OTHER SOURCE(S): MARPAT 130:168387
 AB Pyrimidine derivs. that are irreversible inhibitors of tyrosine kinases are reported. Thus, PhCH2OH was treated with 4-FC6H4NO2 to give 4-chloro-6-nitroquinazoline hydrochloride. The resulting 6-nitro-4-(4-benzoyloxyanilino)quinazoline hydrochloride was reduced to the amine and acylated to give N-(4-(4-benzoyloxyanilino)quinazolin-6-yl)acrylamide (I). I had an IC50 for inhibition of epidermal growth factor receptor tyrosine kinase of 3.6 nM.

IT 220488-46-0P
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of anilinoquinazolinylacrylamides and related compds. as tyrosine kinase inhibitors)

RN 220488-46-0 CAPLUS
 CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[(4-phenoxyphenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

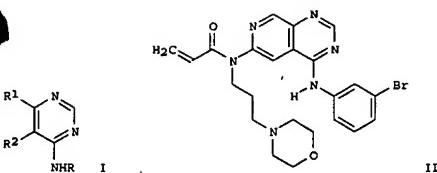
L3 ANSWER 72 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 73 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN
 1997:696745 CAPIUS
 128:3695
 Preparation of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors
 Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; McNamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong; et al.
 Warner-Lambert Company, USA; Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; McNamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong
 PCT Int. Appl., 193 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| WO 9738983 | A1 | 19971023 | WO 1997-US5778 | 19970408 |
| W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CP, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CA 2249446 | AA | 19971023 | CA 1997-2249446 | 19970408 |
| AU 9724463 | A1 | 19971107 | AU 1997-24463 | 19970408 |
| AU 725533 | B2 | 20001012 | | |
| EP 892789 | A1 | 19990127 | EP 1997-920213 | 19970408 |
| EP 892789 | B1 | 20020227 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI | | | | |
| CN 1218456 | A | 19990602 | CN 1997-194458 | 19970408 |
| CN 1145614 | B | 20040414 | | |
| BR 9708640 | A | 19990803 | BR 1997-8640 | 19970408 |
| JP 2000508657 | T2 | 20000711 | JP 1997-537173 | 19970408 |
| JP 3370340 | B2 | 20030127 | | |
| AT 213730 | E | 20020315 | AT 1997-920213 | 19970408 |
| ES 2174250 | T3 | 20021101 | ES 1997-920213 | 19970408 |
| SK 284073 | B6 | 20040908 | SK 1998-1417 | 19970408 |
| ZA 9703060 | A | 19971104 | ZA 1997-3060 | 19970410 |
| BG 63160 | B1 | 20010531 | BG 1998-102811 | 19981001 |
| NO 9804718 | A | 19981209 | NO 1998-4718 | 19981009 |
| KR 2000005364 | A | 20000125 | KR 1998-708086 | 19981010 |
| US 6344459 | B1 | 20020205 | US 1999-155501 | 19990608 |
| US 6602863 | B1 | 20030805 | US 2000-671559 | 20000927 |
| US 2003229051 | A1 | 20031211 | US 2003-441450 | 20030520 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1996-15351P | P 19960412 |
| | | | WO 1997-US5778 | W 19970408 |
| | | | US 1999-155501 | A3 19990608 |
| | | | US 2000-671559 | A3 20000927 |

L3 ANSWER 73 OF 73 CAPIUS COPYRIGHT 2004 ACS on STN (Continued)
 OTHER SOURCE(S): MARPAT 128:3695
 GI

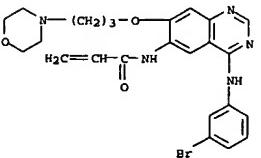
AB Title compds. [I; R = (CHR6)pR9; R1R2 = CH:CR7CR8:CH, CH:CR7CR8:N, CH:CR7:N, etc.; R6 = H or alkyl; 1 of R7,R8 = Z1Z2R10 and the other = OR4, SR4, NHR2; R3,R4 = (un)substituted alkyl, heterocyclicalkyl, etc.; R9 = (un)substituted Ph; R10 = CR11:CHRS, C(=O)pbond.CRS, CR11:C:CR5; R5 = H, halo, alkyl, Ph, etc.; R11 = H, halo, alkyl; Z1 = bond, O, (alkyl)imino, CH2, etc.; Z2 = CO, SO, PO(O)OH, etc.; p = 0 or 1] were prepared. Thus, I (R = C6H4Br-3, R1R2 = CH:NCR8:CH, R8 = F) was condensed with 3-morpholinopropanamine and the product acylated by CH2:CHCOCl to give title compound II. Data for biol. activity of I were given.

198959-99-89

IT RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses); [preparation of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors]

RN 198959-99-8 CAPIUS

CN 2-Propenamide, N-(4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl)- (9CI) (CA INDEX NAME)



10/ 016,280

=> d his

(FILE 'HOME' ENTERED AT 14:07:18 ON 30 NOV 2004)

FILE 'REGISTRY' ENTERED AT 14:07:50 ON 30 NOV 2004

L1 STRUCTURE UPLOADED
L2 422 S L1 FUL

FILE 'CAPLUS' ENTERED AT 14:08:26 ON 30 NOV 2004

L3 73 S L2

=> log y